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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII
Act. 411 PRESENTACION

Dep. 2020 DIR.NUEVASCR
Eve: 378 FASENACIONALI
Folios: 188 189



Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE NUEVAS CREACIONES

SOLICITUD FASE NACIONAL -PCT

21. EXPEDIENTE No. _____

54. TITULO: COMPOSICIÓN FARMACÉUTICA
OFTALMOLÓGICA TÓPICA QUE CONTIENE
REGORAFENIB

51. CLASIFICACION INTERNACIONAL:

A61K 9/00 (2006.01) A61K 31/4412 (2006.01)

A61K 47/02 (2006.01) A61K 47/06 (2006.01)

A61K 47/14 (2006.01) A61K 47/26 (2006.01)

A61K 47/38 (2006.01)

71. SOLICITANTE: BAYER HEALTHCARE LLC

DOMICILIO: 100 Bayer Boulevard Whippany, New Jersey
ESTADOS UNIDOS DE AMERICA

74. APODERADO: HELENA CAMARGO WILLIAMSON

22. BOGOTÁ D.C., DICIEMBRE 26 DE 2013



Industria y Comercio
SUPERINTENDENCIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



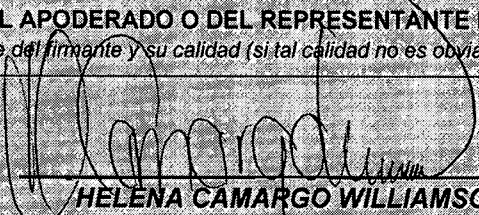
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DIRECCIÓN DE
SOLICITUD FASE NACIONAL –PCT

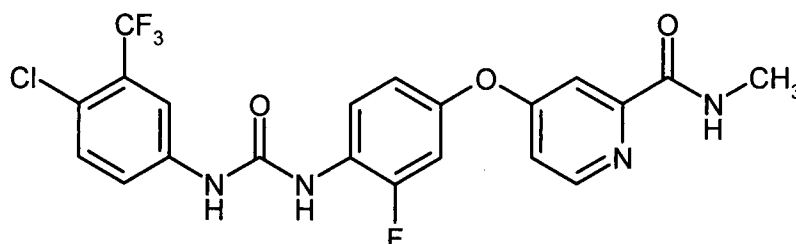
1	TIPO DE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
Solicitud Internacional No.		PCT/EP2012/062365	Fecha 26/06/2012
Publicación Internacional No.		WO 2013/000917 A1	Fecha 03/01/2013
3	TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)		
COMPOSICIÓN FARMACÉUTICA OFTALMOLÓGICA TÓPICA QUE CONTIENE REGORAFENIB			
4	CLASIFICACIÓN INTERNACIONAL (CIP)		
A61K 9/00 (2006.01) A61K 31/4412 (2006.01) A61K 47/02 (2006.01) A61K 47/06 (2006.01) A61K 47/14 (2006.01) A61K 47/26 (2006.01) A61K 47/38 (2006.01)			
SOLICITANTE (S) Esta persona también es inventor Para datos adicionales utilizar hoja de información complementaria			
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PAÍS DE RESIDENCIA ESTADOS UNIDOS DE AMERICA		ESTADOS UNIDOS DE AMERICA	
7	INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria		
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10. Alemania		10. Wuppertal	10. Von-der-Goltz-Str. 7, 42329
OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)			
☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.			

9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS CAMARGO WILLIAMSON		NOMBRES HELENA	IDENTIFICACIÓN C.C 35.455.268 T.P 76985
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CIUDAD	BOGOTÁ		CORREO ELECTRÓNICO helena.camargo@phrlegal.com
PAÍS	COLOMBIA		No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL
10	DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO		
(33) PAÍS DE ORIGEN		CÓDIGO PAÍS	(31) NÚMERO
1. COMUNIDAD EUROPEA			12155281.4
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			(32) FECHA (AAAA/MM/DD) 14/02/2012 28/06/2011
11	DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS		
Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.			
☐ SI ☒ NO			
12	DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES		
Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.			
☐ SI ☒ NO			
13	REDUCCIÓN DE TASAS		
Declaro que carezco de medios económicos para presentar la solicitud de patente.			
☐ SI ☒ NO			
Micro, pequeñas y medianas empresas ☐			
Universidades públicas o privadas ☐			
Entidades sin ánimo de lucro ☐			
Debe aportar los documentos que se indican en el numeral 17 de anexos			
14	AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☒ SI ☐ NO		
Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.			
15	COMPROBANTE DE PAGO O PAGO ELECTRÓNICO	N°	Fecha
16	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL		
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)			
 HELENA CAMARGO WILLIAMSON			
17	ANEXOS		
Documentación Técnica Solicitud Internacional en castellano		Documentación Jurídica	
1. ☒ Descripción N° de folios:		9. ☒ Poderes, si fuera el caso,	
2. ☒ Reivindicaciones N° Reivindicaciones:		10. ☐ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.	
3. ☒ Dibujos y/o figuras N° folios:		11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.	
4. ☒ Resumen.		12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.	
5. ☐ Certificado de depósito de material biológico si fuera el caso.		13. Reducción de tasas	
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.		Micro, pequeñas o medianas empresas	
7. ☐ Arte final 12 x 12.		☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.	
8. ☐ Anexo formato digital.		☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.	
		Universidades públicas o privadas	
		☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación	
		Entidades sin ánimo de lucro	
		☐ Copia de registro vigente en Cámara de comercio.	
		☐ Hoja de información complementaria.	
		☐ Otros, especificar	
		14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.	
		15. ☐ Comprobante de pago por reivindicación de prioridad.	
		16. ☒ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.	
		17. ☒ Comprobante de pago por reivindicación adicional a 10.	

COMPOSICIÓN FARMACÉUTICA OFTALMOLÓGICA TÓPICA QUE
CONTIENE REGORAFENIB

La presente invención se refiere a composiciones farmacéuticas oftalmológicas tópicas que contienen regorafenib, un hidrato, solvato o sal farmacéuticamente aceptable del mismo o un polimorfo del mismo y su
5 procedimiento de preparación y su uso para el tratamiento de trastornos oftalmológicos.

El regorafenib, que es la metilamida del ácido 4{4-[3-(4-cloro-3-trifluorometilfenil)-ureido]-3-fluorofenoxi}piridin-2-carboxílico, un compuesto de
10 fórmula (I)



(I)

es un potente agente anti-cáncer y anti-angiogénico que posee varias actividades, incluyendo actividad inhibitoria sobre el VEGFR, PDGFR, raf, p38,
15 y/o moléculas de señalización flt-3 quinasas y se puede usar en el tratamiento de diversas enfermedades y afecciones como trastornos hiper-proliferativos, tales como cánceres, tumores, linfomas, sarcomas y leucemias como se describe en el documento WO 2005/009961. Además se mencionan sales del compuesto de fórmula (I), tales como su clorhidrato, mesilato y fenilsulfonato,
20 en el documento WO 05/009961. El monohidrato del compuesto de fórmula (I) se menciona en el documento WO 08/043446.

La degeneración macular relacionada con la edad (AMD) es la principal causa de ceguera en la población anciana y es reconocida como AMD seca y húmeda (Expert Opin. Ther. Patents (2010), 20 (1), 103 - 11). La forma seca, o
25 no exudativa, comprende cambios atróficos e hipertróficos del epitelio pigmentario de la retina (RPE). La forma seca se caracteriza por drusas

maculares que son áreas pigmentadas que contienen células muertas y productos metabólicos que distorsionan la retina y, finalmente, causan pérdida de visión aguda. Los pacientes con AMD no exudativa (forma seca) pueden progresar a AMD húmeda, o exudativa o neovascular, en la cual se desarrollan

5 membranas neovasculares coroideas (CNMV) patológicas bajo la retina, pérdida de líquido y sangre y, en última instancia, provocan una cicatriz disciforme cegadora central durante un período de tiempo relativamente corto si no se tratan. La neovascularización coroidea (CNV), el crecimiento de nuevos vasos sanguíneos a partir de la red capilar coroidea a través de la membrana

10 de Bruch/interfaz de RPE en la retina neural, da como resultado desprendimiento de retina, edema subretiniano e intrarretiniano, y cicatrización.

El acceso a la coroides, que se encuentra entre la esclerótica y la retina por una vía distinta a la sangre, es difícil. El ojo se compone de tres compartimentos anatómicos principales, la cámara anterior, la cámara posterior,

15 y la cavidad vítrea, que tienen interacción fisiológica limitada entre sí. La retina se encuentra en la parte posterior de la cavidad vítrea, y está protegida del exterior por la esclerótica, que es la pared blanca, dura, impermeable del ojo. El flujo sanguíneo coroidal es el procedimiento habitual de transporte de sustancias a la coroides y requiere, por ejemplo, administración oral o

20 intravenosa del medicamento. La mayoría de los medicamentos no se pueden suministrar a la coroides mediante gotas oculares o un depósito en la proximidad del ojo. Algunos medicamentos han sido suministrados a la retina y por lo tanto a la coroides por inyección en la cámara vítrea del ojo. El tratamiento de enfermedades oculares posteriores (parte posterior del ojo)

25 mediante formulaciones oculares tópicas de fácil aplicación como gotas oculares sigue siendo un problema sin resolver.

El VEGF (factor de crecimiento endotelial vascular) es una citocina clave en el desarrollo de los vasos sanguíneos normales, así como en el desarrollo de vasos en tumores y otros tejidos sometidos a angiogénesis anormal y parece

desempeñar un papel central en la patogénesis de la formación de CNV (Expert Opin. Ther. Patents (2010), 20(1), 103-118, Expert Opin. Ther. Patents (2009), 18(10), 1573-1580, J. Clin. Invest. (2010), 120(9), 3033-3041, J. Cell. Physiol. (2008), 216, 29-37, New Engl. J. Med. 2006, 355, 1474-1485, WO 2010/127029, WO 2007/064752). Se describen medicamentos que bloquean los efectos del VEGF para el tratamiento de AMD húmeda tales como aptámeros como pegaptanib (New Engl. J. Med. 2004, 351, 2805-2816), o anticuerpos contra VEGF como ranibizumab (New Engl. J. Med. 2006, 355, 1419-1431) o bevacizumab (Ophtalmology, 2006, 113, 363-372). Sin embargo, dichos medicamentos se deben administrar por vía intravítrea por inyección en el ojo. El sorafenib, también un inhibidor de VEGF, se describe para el tratamiento de CNV por administración oral (Clinical and Experimental Ophthalmology, 2010, 38, 718-726). El pazopanib, también un inhibidor de VEGF, se describe para el tratamiento de AMD por administración tópica de gotas oculares que contienen una solución acuosa de Pazopanib (documento WO 2011/009016). El documento WO 2006/133411 describe compuestos para el tratamiento de CNV por administración tópica de formulaciones liposomales. Los documentos WO 2007/076358, US2006257487 describen formulaciones oftalmológicas acuosas para administración tópica. El documento WO 2008/27341 describe emulsiones para administración tópica en el ojo.

Es de conocimiento general de los expertos que usualmente las gotas oculares tópicas no suministran niveles terapéuticos de moléculas de medicamento a tejidos diana presentes en la parte posterior del ojo con el fin de tratar enfermedades oculares posteriores (U.B. Kompella and H.F. Edelhauser, "Drug Product Development for the Back of the Eye", aapspress Springer, 2011, page 449).

A pesar del progreso descrito en la técnica sigue existiendo una necesidad de medicamentos mejorados para el tratamiento de trastornos oftalmológicos como AMD. En particular, sigue existiendo una necesidad de

- composiciones farmacéuticas oftalmológicas tópicas como gotas oculares que se puedan administrar fácilmente y por lo tanto aumentarían el cumplimiento del paciente. Además, existe aún la necesidad de composiciones farmacéuticas oftalmológicas tópicas aplicables para compuestos que tienen por ejemplo una
- 5 baja solubilidad que no se pueden formular en una solución sencilla, emulsión, como un complejo o en una formulación liposomal. La composición farmacéutica oftalmológica tópica debe proporcionar una concentración del agente activo en el ojo que sea suficiente para una terapia efectiva. Esto depende de la solubilidad y el comportamiento de liberación del agente activo.
- 10 En el caso de una formulación líquida las propiedades de disolución y la estabilidad química del agente activo son de importancia. Con el fin de apoyar un alto cumplimiento, la composición farmacéutica oftalmológica tópica no se debería aplicar más de 5 veces al día, mientras menos, mejor. El tipo y cantidad de los excipientes en combinación con el procedimiento de preparación de la
- 15 composición farmacéutica son esenciales para las propiedades de liberación, biodisponibilidad del agente activo en el ojo, en particular en la parte posterior del ojo (por ejemplo, en el área de la retina, membrana de Bruch y coroides), estabilidad, compatibilidad, eficacia y aplicabilidad industrial del procedimiento de fabricación de la composición farmacéutica oftalmológica tópica.
- 20 El problema a resolver por la presente invención es proporcionar una composición farmacéutica oftalmológica tópica que comprenda regorafenib como agente activo, que tenga una estabilidad y compatibilidad suficientes y que alcance una concentración efectiva de regorafenib en el ojo, en particular en la parte posterior del ojo para el tratamiento de trastornos oftalmológicos con
- 25 suficiente eficacia, evitando una administración intravenosa u oral o inyección en o cerca del ojo (por ejemplo, inyecciones intravítreas u otras).

Otro problema a resolver por la presente invención es proporcionar una composición farmacéutica oftalmológica tópica para el tratamiento de una enfermedad ocular posterior.

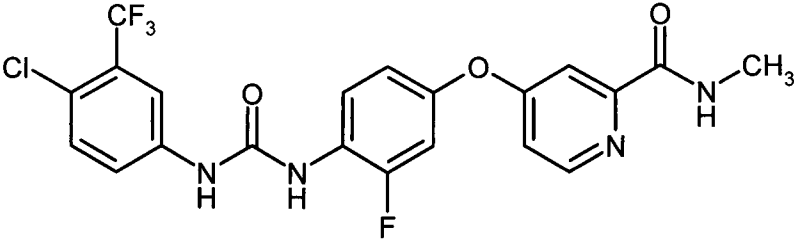
El monohidrato de regorafenib tiene un perfil de solubilidad limitado. La solubilidad termodinámica del monohidrato de regorafenib en diferentes disolventes se muestra en la Tabla 1:

Tabla 1:

Disolvente	Solubilidad (mg/ml)
Agua	< 0,1
Parafina líquida liviana	< 0,1
Etanol	6,4
Polietilenglicol (PEG) 400	67,3
HPβ-Ciclodextrina/agua (10:90)	< 0,1
PEG 400/agua (30:70)	0,27
Glicéridos de oleilpolietilenglicol	3,6

Sorprendentemente, la composición farmacéutica de acuerdo con la invención proporciona por administración tópica una cantidad suficiente del agente activo en el ojo que es efectiva para tratar trastornos oftalmológicos. En particular, la composición farmacéutica de acuerdo con la invención proporciona el agente activo en una cantidad suficiente en la parte posterior del ojo, es decir, que la composición farmacéutica de acuerdo con la invención realiza el transporte del agente activo desde la parte frontal del ojo a la parte posterior del ojo. Además, la composición farmacéutica de acuerdo con la invención tiene una estabilidad suficiente sin ninguna degradación significativa del agente activo y es compatible con el ojo.

La presente invención se refiere a una composición farmacéutica oftalmológica tópica que comprende regorafenib, el compuesto de la fórmula (I),



(I)

un hidrato, solvato o sal farmacéuticamente aceptable de regorafenib, o un polimorfo del mismo y al menos un vehículo farmacéuticamente aceptable y opcionalmente al menos un excipiente farmacéuticamente aceptable.

- 5 Se da preferencia a una composición farmacéutica oftalmológica tópica que comprende regorafenib, un hidrato, solvato o sal farmacéuticamente aceptable de regorafenib o un polimorfo del mismo como agente activo y al menos un vehículo farmacéuticamente aceptable y opcionalmente al menos un excipiente farmacéuticamente aceptable, siendo la composición una suspensión
- 10 que comprende el agente activo suspendido en el vehículo farmacéuticamente aceptable aplicable.

Un vehículo o excipiente farmacéuticamente aceptable es cualquier vehículo o excipiente que es relativamente no tóxico e inocuo para un paciente a concentraciones consistentes con la actividad efectiva del agente activo, de modo que cualquier efecto secundario atribuible al vehículo o excipiente no vicia

15 los efectos beneficiosos del agente activo.

La expresión "el compuesto de fórmula (I)" o "regorafenib" se refiere a 4-{4-[[{4-cloro-3-(trifluorometil)fenil]amino}carbonil]-amino]-3-fluorofenoxi}-N-metilpiridin-2-carboxamida como se representa en la fórmula (I).

- 20 La expresión "compuesto de la invención" o "agente activo" se refiere a regorafenib, un hidrato, solvato o sal farmacéuticamente aceptable de regorafenib, o un polimorfo del mismo.

Los solvatos para los fines de la invención son aquellas formas de los compuestos o sus sales, en las que las moléculas del disolvente forman un complejo estequiométrico en el estado sólido e incluyen pero no se limitan a, por ejemplo, etanol y metanol.

25

Los hidratos son una forma específica de solvatos, en los que la molécula de disolvente es agua. Los hidratos de los compuestos de la invención o sus sales son composiciones estequiométricas de los compuestos o sales con

agua, tales como, por ejemplo, hemi-, mono- o dihidratos. Se da preferencia al monohidrato de regorafenib.

Las sales para los fines de la presente invención son preferentemente sales farmacéuticamente aceptables de los compuestos de acuerdo con la invención. Las sales farmacéuticamente aceptables son bien conocidas por aquellos expertos en la técnica e incluyen sales de ácidos inorgánicos y orgánicos, tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido metanosulfónico, ácido trifluorometanosulfónico, ácido bencenosulfónico, ácido p-tolueno sulfónico (sal de tosilato), ácido 1-naftalenosulfónico, ácido 2-naftalenosulfónico, ácido acético, ácido trifluoroacético, ácido málico, ácido tartárico, ácido cítrico, ácido láctico, ácido oxálico, ácido succínico, ácido fumárico, ácido maleico, ácido benzoico, ácido salicílico, ácido fenilacético y ácido mandélico. Además, las sales farmacéuticamente aceptables incluyen sales de bases inorgánicas, tales como sales que contienen cationes alcalinos (por ejemplo, Li^+ , Na^+ o K^+), cationes alcalino-térreos (por ejemplo, Mg^{+2} , Ca^{+2} o Ba^{+2}), el catión amonio, así como sales ácidas de bases orgánicas, incluyendo cationes amonio sustituidos alifáticos y aromáticos, y cationes de amonio cuaternario, tales como las derivadas de protonación o peralquilación de trietilamina, *N,N*-dietilamina, *N,N*-d ciclohexilamina, lisina, piridina, *N,N*-dimetilaminopiridina (DMAP), 1,4-diazabiclo[2.2.2]octano (DABCO), 1,5-diaza-biciclo[4.3.0]non-5-eno (DBN) y 1,8-diazabiclo[5.4.0]undec-7-eno (DBU). Se da preferencia a la sal de clorhidrato, mesilato o fenilsulfonato de regorafenib.

Se prefieren regorafenib y el monohidrato de regorafenib, el más preferente es el monohidrato de regorafenib como compuestos de la presente invención.

Debido a la baja solubilidad de regorafenib, en particular del monohidrato de regorafenib (véase tabla 1) las soluciones estándar no son aplicables. Tampoco las soluciones que contienen cantidades tolerables de emulsionantes,

agentes solubilizantes, excipientes formadores de complejos, etc. están disponibles para proporcionar, por ejemplo, estabilidad suficiente del regorafenib.

La composición farmacéutica oftalmológica tópica de acuerdo con la invención comprende el compuesto de la invención, preferentemente regorafenib, más preferentemente monohidrato de regorafenib en una forma sólida, preferentemente en una forma cristalina, más preferentemente en una forma microcristalina.

La micronización se puede llevar a cabo por procedimientos estándar de molienda, preferentemente por molienda por chorro de aire, conocida para una persona experta. La forma microcristalina puede tener un tamaño medio de partícula de desde 0,5 a 10 μm , preferentemente de 1 a 6 μm , más preferentemente de 1 a 3 μm . El tamaño de partícula indicado es la media de la distribución del tamaño de partícula medida por difracción láser conocida para una persona experta (dispositivo de medición: HELOS, Sympatec).

La concentración mínima del compuesto de la invención, preferentemente regorafenib, más preferentemente monohidrato de regorafenib, en la composición farmacéutica oftalmológica tópica es de 0,01%, preferentemente 0,2% en peso de la cantidad total de la composición. La concentración máxima del compuesto de la invención, preferentemente regorafenib, más preferentemente monohidrato de regorafenib, en la composición farmacéutica oftalmológica tópica es del 10%, preferentemente del 5%, más preferentemente del 4% en peso de la cantidad total de la composición.

Se da preferencia a una concentración del compuesto de la presente invención en la composición farmacéutica de 0,1 a 100 mg/ml, preferentemente de 1 a 50 mg/ml, más preferentemente de 2 a 40 mg/ml.

Se da particular preferencia a una concentración de regorafenib en la composición farmacéutica de 0,1 a 100 mg/ml, preferentemente de 1 a 50 mg/ml, más preferentemente de 2 a 40 mg/ml.

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Se da particular preferencia a una composición farmacéutica que resulta de la adición de monohidrato regorafenib en cantidades de 0,1 a 100 mg/ml, preferentemente de 1 a 50 mg/ml, más preferentemente de 2 a 40 mg/ml.

La composición farmacéutica oftalmológica tópica de acuerdo con la invención incluye pero no se limita a gotas, geles, pomadas, dispersiones o suspensiones oculares.

Se da preferencia a una composición farmacéutica oftalmológica tópica que es una suspensión.

El compuesto de la invención, preferentemente regorafenib, más preferentemente monohidrato de regorafenib, se utiliza preferentemente en una forma micronizada.

La micronización se puede lograr por procedimientos estándar de molienda, preferentemente por molienda por chorro de aire, conocida para una persona experta. La forma micronizada puede tener un tamaño medio de partícula de desde 0,5 a 10 μm , preferentemente de 1 a 6 μm , más preferentemente de 2 a 3 μm . El tamaño de partícula indicado es la media de la distribución del tamaño de partícula medida por difracción láser conocida para una persona experta (dispositivo de medición: HELOS, Sympatec).

Una realización de la presente invención es una composición farmacéutica oftalmológica tópica que es una suspensión que comprende el compuesto de la invención, preferentemente regorafenib, más preferentemente monohidrato de regorafenib en una forma sólida, preferentemente en una forma cristalina, más preferentemente en una forma cristalina microfina suspendida en un vehículo farmacéuticamente aceptable aplicable y, opcionalmente, que comprende además uno o más excipientes farmacéuticamente aceptables.

Se da preferencia a una suspensión basada en un vehículo no acuoso, más preferentemente a una suspensión basada en un vehículo hidrófobo.

Los vehículos farmacéuticamente aceptables adecuados de acuerdo con la presente invención incluyen pero no están limitados a glicéridos de oleoil

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polietilenglicol, glicéridos de linoleoil polietilenglicol, glicéridos de lauroil polietilenglicol, vehículos hidrocarburos como parafina líquida (Paraffinum liquidum, aceite mineral), parafina líquida liviana (parafina de baja viscosidad, Paraffinum perliquidum, aceite mineral ligero), parafina blanda (vaselina),
5 parafina dura, aceites grasos vegetales como aceite de ricino, aceite de cacahuete o aceite de sésamo, aceites grasos sintéticos como triglicéridos de cadena media (MCT, triglicéridos con ácidos grasos saturados, preferentemente ácido octanoico y decanoico), miristato de isopropilo, glicérido de caprilcaproil macrogol-8, glicéridos de caprilcaproil polioxil-8, alcoholes de lanolina como
10 alcoholes cetilestearílicos, lanolina, glicerol, propilenglicol, diésteres de propilenglicol de ácido caprílico/cáprico, polietilenglicoles (PEG) o una mezcla de los mismos.

Se da preferencia a vehículos no acuosos farmacéuticamente aceptables, que incluyen pero no están limitados a triglicéridos de cadena media (MCT, triglicéridos con ácidos grasos saturados, preferentemente ácido octanoico y
15 decanoico, miristato de isopropilo, glicérido de caprilcaproil macrogol-8, glicéridos de caprilcaproil polioxil-8, glicéridos de oleoil polietilenglicol, glicéridos de oleoil macrogol-6 (Labrafil M 1944 CS), glicéridos de linoleoil macrogol-6 (Labrafil M2125 CS = glicéridos de linoleoil polioxil-6), glicéridos de
20 lauroil macrogol-6 (Labrafil M 2130 CS = glicéridos de lauroil polioxil-6)), vehículos hidrocarburos, aceites grasos como aceite de ricino o una mezcla de los mismos. Más preferentemente se usan vehículos hidrófobos como vehículos de hidrocarburos que incluyen pero no se limitan a parafina líquida o parafina líquida liviana o una mezcla de las mismas.

25 Muy sorprendentemente la suspensión de acuerdo con la presente invención, que comprende un vehículo lipófilo como parafina líquida o parafina líquida liviana, proporciona mediante administración tópica una cantidad suficiente del agente activo a la parte posterior del ojo que es efectiva para

tratar trastornos oftalmológicos, aunque la solubilidad del monohidrato de regorafenib en vehículos lipófilos es muy baja.

El vehículo farmacéuticamente aceptable es la base de la composición farmacéutica oftalmológica tópica de acuerdo con la presente invención y está
5 presente en la composición en una concentración mínima del 75%, preferentemente 80%, más preferentemente 85% y en una concentración máxima de 99,9%, preferentemente 99%, más preferentemente 98% en peso de la cantidad total de la composición.

La composición farmacéutica según la presente invención puede tener
10 diferentes viscosidades, de modo que, en principio, es concebible una gama de sistema de baja viscosidad a pastas. Se da preferencia a sistemas fluidos que incluyen sistemas de baja viscosidad y también sistemas de mayor viscosidad siempre y cuando aún fluyan bajo su propio peso.

Otros excipientes farmacéuticamente aceptables adecuados usados en la
15 composición farmacéutica oftalmológica tópica de acuerdo con la presente invención incluyen pero no se limitan a estabilizadores, tensioactivos, vehículos basados en polímeros como agentes gelificantes, co-disolventes orgánicos, componentes activos de pH, componentes activos osmóticos y conservantes.

Los estabilizantes adecuados usados en la composición farmacéutica
20 oftalmológica tópica de acuerdo con la presente invención incluyen pero no se limitan a sílice coloidal, sílices hidrófilas e hidrófobas.

Se da preferencia a sílices hidrófobas que son sílices que no son mojadas por el agua; esto significa que flotan en la superficie del agua. Asimismo son adecuados los óxidos mixtos hidrofobizados de dióxido de silicio
25 y óxido de aluminio, pero se prefieren sílices puras hidrófobas. Las mismas se producen por la mezcla de sílice hidrófila con silanos (halosilanos, alcoxisilanos, silazanos, siloxanos). Esto implica grupos silanol que son alquilados por grupos alquilo que tienen preferentemente uno hasta 18 átomos de carbono, en particular que tienen preferentemente uno hasta 8 átomos de carbono, en

particular que tienen muy preferentemente hasta 4 átomos de carbono, especialmente por grupos metilo. Los ejemplos de silanos usados en la producción de sílices hidrófobas son hexametildisilazano o, preferentemente, dimetildiclorosilano. Las sílices hidrófobas apropiadas pueden derivar de sílices
5 precipitadas, coloidales, precompactadas o pirogénicas, con preferencia para sílices pirogénicas. Por ejemplo, la reacción de una sílice hidrófila con dimetildiclorosilano resulta en Aerosil hidrófobo que tiene el nombre registrado Aerosil® R 972; este tiene un grado de metilación de 66% a 75% (determinado mediante titulación de los grupos silanol remanentes).

10 La sílice hidrófoba se emplea en las formulaciones comúnmente en una proporción de 0,1 a 10% en peso, preferentemente empleada con 0,5 a 5%, por ejemplo, con 2%, en peso de la composición total. Otros agentes estabilizantes y/o gelificantes adecuados usados en la composición farmacéutica oftálmica tópica de acuerdo con la presente invención incluyen pero no están limitados a
15 monopalmitoestearato de propilenglicol, monoestearato de glicerilo, dibehenato de glicerilo, diestearato de glicerilo, grasa dura, polivinilpirrolidona, polietileno, glicerol, estearatos de polioxietileno, ésteres de ácidos grasos de sorbitán, colesterol, glicerolmonoestearato de macrogol-20, poloxámero 124, miristato de isopropilo, palmitato de isopropilo, sílice coloidal, sílice coloidal hidrófoba,
20 estearato de magnesio, estearato de zinc, estearato de aluminio, alcoholes de lanolina, arcillas orgánicas, vaselina, estearato de polioxil 6.

Los tensioactivos adecuados usados en la composición farmacéutica oftalmológica tópica de acuerdo con la presente invención incluyen pero no se limitan a lípidos tales como fosfolípidos, fosfatidilcolinas, lecitina, cardiolipinas,
25 ácidos grasos, fosfatidiletanolaminas, fosfátidos, tiloxapol, polietilenglicoles y derivados como PEG 400, PEG 1500, PEG 2000, poloxámero 407, poloxámero 188, polisorbato 80, polisorbato 20, laurato de sorbitán, estearato de sorbitán, palmitato de sorbitán o una mezcla de los mismos, preferentemente polisorbato 80.

Los vehículos en base a polímeros adecuados como agentes gelificantes usados en la composición farmacéutica oftalmológica tópica de acuerdo con la presente invención incluyen pero no se limitan a celulosa, hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), carboximetil
5 celulosa (CMC), metilcelulosa (MC), hidroxietilcelulosa (HEC), amilasa y derivados, amilopectinas y derivados, dextrano y derivados, polivinilpirrolidona (PVP), alcohol polivinílico (PVA), y polímeros acrílicos tales como los derivados de ácido poliacrílico o polimetacrílico como HEMA, carbopol y derivados de los antes mencionados o una mezcla de los mismos.

10 Los co-disolventes orgánicos adecuados usados en la composición farmacéutica de acuerdo con la invención incluyen pero no están limitados a etilenglicol, propilenglicol, N-metil pirrolidona, 2-pirrolidona, 3-pirrolidinol, 1,4-butanodiol, dimetilglicol monometiléter, dietilenglicol monometiléter, solcetal, glicerol, polietilenglicol, polipropilenglicol.

15 Los componentes activos de pH adecuados, tales como agentes tamponantes o agentes de ajuste de pH usados en la composición farmacéutica de acuerdo con la invención, incluyen pero no están limitados a fosfato disódico, fosfato monosódico, ácido bórico, borato de sodio, citrato de sodio, ácido clorhídrico, hidróxido de sodio.

20 Los componentes activos de pH se eligen basándose en el pH previsto para la composición que generalmente abarca entre pH 4 a 9.

Los componentes activos osmóticos adecuados usados en la composición farmacéutica de acuerdo con la invención incluyen pero no están limitados a cloruro de sodio, manitol, glicerol.

25 Los conservantes usados en la composición farmacéutica de acuerdo con la invención incluyen pero no están limitados a cloruro de benzalconio, cloruro de alquildimetilbencilamonio, cetrimida, cloruro de cetilpiridinio, bromuro benzododecinio, cloruro de bencetonio, tiomersal, clorobutanol, alcohol

bencílico, fenoxetanol, alcohol feniletílico, ácido sórbico, metil y propil parabenos, digluconato de clorhexidina, EDTA o mezclas de los mismos.

Los agentes gelificantes, agentes activos de pH y agentes activos osmóticos se utilizan preferentemente en el caso de un vehículo acuoso
5 farmacéuticamente aceptable.

La cantidad del excipiente farmacéuticamente aceptable adecuado adicional en la suspensión de acuerdo con la presente invención puede ser de 0,1 a 15%, preferentemente de 0,5 a 10%, más preferentemente de 1 a 5% en el peso total de la suspensión.

10 Preferentemente, la cantidad de hidroxipropilmetilcelulosa en la suspensión de acuerdo con la presente invención puede ser de 0,05 a 15%, preferentemente de 0,1 a 10%, más preferentemente de 1 a 5% en el peso total de la suspensión.

Preferentemente, la cantidad de polisorbato 80 en la suspensión de
15 acuerdo con la presente invención puede ser de 0,05 a 10%, preferentemente de 0,1 a 7%, más preferentemente de 0,5 a 4% en el peso total de la suspensión.

Se da preferencia a una composición farmacéutica oftalmológica tópica que comprende monohidrato de regorafenib cristalino, más preferentemente
20 monohidrato de regorafenib microcristalino en una concentración de por ejemplo 0,01 a 10%, más preferentemente de 0,2 a 5% en peso de la cantidad total de la composición suspendida en un vehículo farmacéuticamente aceptable seleccionado del grupo que comprende parafina líquida, parafina líquida liviana o una mezcla de las mismas que contiene opcionalmente sílice
25 hidrófoba como estabilizador en una cantidad de 0,1% a 10%, preferentemente 0,5 a 5%, por ejemplo, con 2% en peso de la composición total.

También se da preferencia a una composición farmacéutica oftalmológica tópica que comprende monohidrato de regorafenib cristalino, más preferentemente monohidrato de regorafenib cristalino microfino en una

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concentración de por ejemplo 0,1 a 10%, más preferentemente de 0,2 a 5% en peso de la cantidad total de la composición suspendida en glicérido de oleoil polietilenglicol como vehículo farmacéuticamente aceptable que contiene opcionalmente sílice hidrófoba como estabilizador en una cantidad de 0,1% a 5 10%, preferentemente 0,5 a 5%, por ejemplo, con 2% en peso de la composición total.

La cantidad total del agente activo a ser administrado por vía tópica en el ojo usando la composición farmacéutica de la presente invención variará generalmente de aproximadamente 0,01 a 50 mg, preferentemente de 0,02 a 10 10 mg, más preferentemente de 0,05 a 5 mg por administración y por ojo. Sobre la base de técnicas de laboratorio estándar conocidas para evaluar compuestos útiles para el tratamiento de trastornos oftalmológicos, mediante ensayos farmacológicos estándar para la determinación del tratamiento de las afecciones identificadas anteriormente en mamíferos, y mediante comparación 15 de estos resultados con los resultados de medicamentos conocidos que se utilizan para tratar estas afecciones, la dosificación efectiva de las composiciones farmacéuticas de esta invención se pueden determinar fácilmente por los expertos en la técnica. La cantidad del ingrediente activo administrado puede variar ampliamente de acuerdo con consideraciones tales 20 como el compuesto particular y la unidad de dosificación empleada, el modo y tiempo de administración, el período de tratamiento, la edad, sexo y condición general del paciente tratado, la naturaleza y extensión de la afección tratada, la tasa de metabolismo y excreción del medicamento, las posibles combinaciones de medicamentos e interacciones entre medicamentos, y similares.

25 La composición farmacéutica de acuerdo con la invención se administra una o más, preferentemente hasta 5, más preferentemente hasta 3 veces por día.

El procedimiento de administración común de la composición farmacéutica de acuerdo con la invención es la administración tópica en el ojo.

No obstante, en algunos casos puede ser ventajoso desviarse de las cantidades especificadas, dependiendo de la respuesta individual al ingrediente activo, el tipo de preparación y el tiempo o intervalo en el que se efectúa la administración. Por ejemplo, menos de las cantidades mínimas antes
5 mencionadas pueden ser suficientes en algunos casos, mientras que el límite superior especificado se debe superar en otros casos. En el caso de la administración de cantidades relativamente grandes, puede ser aconsejable dividir éstas en varias dosis individuales a lo largo del día.

Esta composición farmacéutica se utilizará para obtener el efecto
10 farmacológico deseado mediante administración tópica preferentemente en el ojo para un paciente en necesidad del mismo, y tendrá propiedades ventajosas en términos de liberación de medicamento, biodisponibilidad, y/o cumplimiento en mamíferos. Un paciente, para el propósito de esta invención, es un mamífero, incluyendo un ser humano, en necesidad de tratamiento para la
15 afección o enfermedad en particular.

La composición farmacéutica de acuerdo con la invención es químicamente estable durante más de 18 meses, preferentemente más de 24 meses. Químicamente estable de acuerdo con la presente invención significa que el agente activo no se degrada significativamente (<1%) durante el
20 almacenamiento.

En este contexto, la composición farmacéutica oftalmológica tópica de acuerdo con la invención contiene metilamida del ácido 4-(4-amino-3-fluorofenoxi)piridin-2-carboxílico (IUPAC: 4-(4-amino-3-fluorofenoxi)-N-metilpiridina-2-carboxamida) (AFP-PMA) en una cantidad igual o menor que
25 0,05%, lo que significa de 0,001% a un máximo de 0,05%, preferentemente en una cantidad igual o menor que 0,025%, lo que significa de 0,001% a un máximo de 0,025%, más preferentemente en una cantidad igual o menor que 0,01%, lo que significa de 0,001% a un máximo de 0,01% en peso basado en la cantidad del compuesto de la fórmula (I).

Procedimiento para fabricación

Se pueden usar varios procedimientos para preparar la composición farmacéutica oftalmológica de acuerdo con la invención. En primer término, el vehículo farmacéuticamente aceptable se prepara mezclando opcionalmente el

5 vehículo o mezcla de vehículos aplicable con los excipientes farmacéuticamente aceptables. Posteriormente, el agente activo se dispersa o suspende en dicha mezcla. El procedimiento también puede incluir esterilización, por ejemplo, por esterilización por precipitación, irradiación gamma, filtración esterilización por filtración, esterilización por calor, llenado aséptico, o una combinación de tales

10 pasos opcionales.

La presente invención se refiere también a un procedimiento para la fabricación de una composición farmacéutica oftalmológica tópica de acuerdo con la invención, en el que el compuesto de la presente invención se suspende en un vehículo farmacéuticamente aceptable aplicable opcionalmente en

15 presencia de uno o más excipientes farmacéuticamente aceptables adicionales y se homogeniza la suspensión.

Se da preferencia a un procedimiento para la fabricación de una composición farmacéutica oftalmológica tópica de acuerdo con la invención en el que

- 20 a) el vehículo farmacéuticamente aceptable aplicable o una mezcla de vehículos farmacéuticamente aceptables aplicables se prepara mezclando los vehículos, opcionalmente en presencia de uno o más excipientes farmacéuticamente aceptables adicionales,
- b) el compuesto de la presente invención, preferentemente
- 25 regorafenib, más preferentemente regorafenib monohidrato, se suspende en dicho vehículo o mezcla farmacéuticamente aceptable aplicable, por ejemplo, a temperatura ambiente, opcionalmente en presencia de uno o más excipientes farmacéuticamente aceptables adicionales,

- c) la suspensión se homogeniza agitando, sacudiendo o mezclando en un mezclador de vórtice, preferentemente agitando, a temperatura ambiente,
- d) la suspensión se subdivide en unidades individuales y se introduce en viales, un recipiente, tubo, frasco, cuentagotas y/o jeringa aplicables.

Opcionalmente en la etapa a) los uno o más excipientes farmacéuticamente aceptables adicionales se añaden al vehículo farmacéuticamente aceptable aplicable a temperaturas elevadas, por ejemplo de 40 a 70 °C.

Procedimiento de tratamiento de trastornos oftalmológicos

La presente invención se refiere también a un uso de la composición farmacéutica de acuerdo con la invención para tratar o prevenir trastornos oftalmológicos.

Además, la presente invención se refiere también a un procedimiento para tratar o prevenir un trastorno oftalmológico que comprende administrar una composición farmacéutica que contiene una cantidad farmacéuticamente efectiva de un agente activo de acuerdo con la presente invención.

Los ejemplos de trastornos oftalmológicos de acuerdo con la invención incluyen, pero no se limitan a degeneración macular relacionada con la edad (AMD), neovascularización coroidea (CNV), membrana neovascular coroidea (CNMV), edema macular quístico (CME), membrana epirretiniana (ERM) y agujero macular, neovascularización coroidea asociada con miopía, estrías vasculares, desprendimiento de retina, retinopatía diabética, edema macular diabético (DME), cambios atróficos del epitelio pigmentario de la retina (RPE), cambios hipertróficos del epitelio pigmentario de la retina (RPE), oclusión venosa de la retina, oclusión de vena coroidea de la retina, edema macular, edema macular por oclusión venosa de la retina, retinitis pigmentaria, enfermedad de Stargardt, glaucoma, afecciones inflamatorias del ojo como por

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ejemplo, uveítis, escleritis o endoftalmitis, cataratas, anomalías refractivas como por ejemplo, miopía, hipermetropía o astigmatismo y queratocono y retinopatía del prematuro. Además, los ejemplos incluyen pero no se limitan a angiogénesis en la parte frontal del ojo como angiogénesis corneal siguiente a por ejemplo, queratitis, trasplante de córnea o queratoplastia, angiogénesis corneal debida a hipoxia (uso extenso de lentes de contacto), pterigión conjuntival, edema subretiniano y edema intrarretiniano. Los ejemplos de degeneración macular relacionada con la edad (AMD) incluyen pero no se limitan a AMD seca o no exudativa, o AMD húmeda o exudativa o neovascular.

10 Se da preferencia a degeneración macular relacionada con la edad (AMD), como AMD seca, AMD húmeda o neovascularización coroidea (CNV).

Otra realización de la presente invención es una composición farmacéutica oftalmológica tópica para el tratamiento o prevención de una enfermedad ocular posterior en la que la composición es una suspensión que comprende un agente activo aplicable para el tratamiento o prevención de una enfermedad ocular posterior suspendida en un vehículo farmacéuticamente aceptable aplicable.

Se da preferencia a una suspensión basada en un vehículo no acuoso, más preferentemente a una suspensión basada en un vehículo hidrófobo.

20 Los ejemplos de enfermedades oculares posteriores incluyen pero no se limitan a degeneración macular relacionada con la edad (AMD), neovascularización coroidea (CNV), membrana neovascular coroidea (CNMV), edema macular quístico (CME), membrana epirretiniana (ERM) y agujero macular, neovascularización coroidea asociada con miopía, estrías vasculares, desprendimiento de retina, retinopatía diabética, edema macular diabético (DME), cambios atróficos del epitelio pigmentario de la retina (RPE), cambios hipertróficos del epitelio pigmentario de la retina (RPE), oclusión venosa de la retina, oclusión de vena coroidea de la retina, edema macular, edema macular

por oclusión venosa de la retina, retinitis pigmentaria, enfermedad de Stargardt y retinopatía del prematuro.

Los ejemplos preferentes de enfermedades oculares posteriores incluyen degeneración macular relacionada con la edad (AMD) como AMD seca, AMD
5 húmeda o neovascularización coroidea (CNV).

Los ejemplos de degeneración macular relacionada con la edad (AMD) incluyen pero no se limitan a AMD seca o no exudativa, o AMD húmeda o exudativa o neovascular.

Los agentes activos aplicables para el tratamiento o prevención de una
10 enfermedad ocular posterior de acuerdo con la presente invención incluyen pero no se limitan a quinasas de receptores dirigidos a inhibidores de transducción de señales de las familias de dominios de, por ejemplo VEGFR, PDGFR, FGFR y sus ligandos respectivos u otros inhibidores de rutas como VEGF-Trap (aflibercept), pegaptanib, ranibizumab, pazopanib, bevasiranib, KH-902,
15 mecamilamina, PF-04523655, E-10030, ACU-4429, volociximab, sirolimus, fenretinida, disulfiram, sonepcizumab, regorafenib, sorafenib y/o tandospirona. Estos agentes incluyen, sin carácter limitante, anticuerpos como Avastina (bevacizumab). Estos agentes también incluyen, sin carácter limitante, inhibidores de moléculas pequeñas como STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol.,
20 Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1),
25 abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518

(Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539), PKC412, nepafenac.

Se da preferencia a regorafenib, bevacizumab, aflibercept, pegaptanib,
5 ranibizumab, pazopanib y/o bevasiranib.

Los vehículos farmacéuticamente aceptables adecuados de acuerdo con la presente invención incluyen pero no están limitados a glicéridos de oleoil polietilenglicol, glicéridos de linoleoil polietilenglicol, glicéridos de lauroil polietilenglicol, vehículos hidrocarburos como parafina líquida (Paraffinum liquidum, aceite mineral), parafina líquida liviana (parafina de baja viscosidad, Paraffinum perliquidum, aceite mineral liviano), parafina blanda (vaselina),
10 parafina dura, aceites grasos vegetales como aceite de ricino, aceite de cacahuete o aceite de sésamo, aceites grasos sintéticos como triglicéridos de cadena media (MCT, triglicéridos con ácidos grasos saturados, preferentemente
15 ácido octanoico y decanoico), miristato de isopropilo, glicérido de caprilcaproil macrogol-8, glicéridos de caprilcaproil polioxil-8, alcoholes de lanolina como alcoholes cetilestearílicos, lanolina, glicerol, propilenglicol, diésteres de propilenglicol de ácido caprílico/cáprico, polietilenglicoles (PEG) o una mezcla de los mismos.

20 Se da preferencia a vehículos no acuosos farmacéuticamente aceptables, que incluyen pero no están limitados a triglicéridos de cadena media (MCT, triglicéridos con ácidos grasos saturados, preferentemente ácido octanoico y decanoico, miristato de isopropilo, glicérido de caprilcaproil macrogol-8, glicéridos de caprilcaproil polioxil-8, glicéridos de oleoil polietilenglicol,
25 glicéridos de oleoil macrogol-6 (Labrafil M 1944 CS), glicéridos de linoleoil macrogol-6 (Labrafil M2125 CS = glicéridos de linoleoil polioxil-6), glicéridos de lauroil macrogol-6 (Labrafil M 2130 CS = glicéridos de lauroil polioxil-6)), vehículos hidrocarburos, aceites grasos como aceite de ricino o una mezcla de los mismos. Muy preferentemente se usan vehículos hidrófobos como vehículos

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de hidrocarburos que incluyen pero no se limitan a parafina líquida o parafina líquida liviana o una mezcla de las mismas.

Muy sorprendentemente la suspensión de acuerdo con la presente invención que comprende un vehículo lipófilo como parafina líquida o parafina líquida liviana proporciona mediante administración tópica una cantidad
5 suficiente del agente activo a la parte posterior del ojo que es efectiva para tratar una enfermedad ocular posterior.

Otros excipientes farmacéuticamente aceptables adecuados usados en la composición farmacéutica oftalmológica tópica de acuerdo con la presente invención incluyen pero no se limitan a estabilizadores, tensioactivos, vehículos
10 basados en polímeros como agentes gelificantes, co-disolventes orgánicos, componentes activos de pH, componentes activos osmóticos y conservantes.

Los estabilizantes adecuados usados en la composición farmacéutica oftalmológica tópica de acuerdo con la presente invención incluyen pero no se
15 limitan a sílice coloidal, sílices hidrófilas y sílices hidrófobas.

Se da preferencia a sílices hidrófobas.

El vehículo farmacéuticamente aceptable es la base de la composición farmacéutica oftalmológica tópica de acuerdo con la presente invención y está presente en la composición en una concentración mínima del 75%,
20 preferentemente 80%, más preferentemente 85% y en una concentración máxima de 99,9%, preferentemente 99%, más preferentemente 98% en peso de la cantidad total de la composición. El ingrediente activo usado en la composición farmacéutica oftalmológica tópica se usa preferentemente en una forma micronizada.

25 La micronización se puede lograr por procedimientos estándar de molienda, preferentemente por molienda por chorro de aire, conocida para una persona experta. La forma micronizada puede tener un tamaño medio de partícula de desde 0,5 a 10 μm , preferentemente de 1 a 6 μm , más preferentemente de 2 a 3 μm . El tamaño de partícula indicado es la media de la

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distribución del tamaño de partícula medido por difracción láser conocida para una persona experta (dispositivo de medición: HELOS, Sympatec).

La concentración del ingrediente activo en la composición farmacéutica es de 0,1 a 100 mg/ml, preferentemente de 1 a 50 mg/ml, más preferentemente
5 de 2 a 40 mg/ml.

La composición farmacéutica de acuerdo con la invención se puede administrar como la única composición farmacéutica o en combinación con una o más de otras composiciones farmacéuticas o agentes activos en los que la combinación no causa efectos adversos inaceptables.

10 "Combinación" significa para los propósitos de la invención no sólo una forma farmacéutica que contiene todos los agentes activos (denominada combinaciones fijas) y paquetes de combinación que contienen los agentes activos separados uno de los otros, sino también agentes activos que se administran simultánea o secuencialmente, siempre y cuando se empleen para
15 la profilaxis o tratamiento de la misma enfermedad.

Como la combinación de acuerdo con la invención es bien tolerada y es potencialmente efectiva incluso en dosis bajas, es posible una amplia gama de variantes de formulación. Por lo tanto, una posibilidad es formular los ingredientes activos individuales de la combinación de acuerdo con la invención
20 por separado. En este caso, no es absolutamente necesario que los ingredientes activos individuales sean tomados al mismo tiempo; por el contrario, la ingesta secuencial puede ser ventajosa para alcanzar efectos óptimos. Es apropiado con tal administración separada combinar las formulaciones de los ingredientes activos individuales tomados
25 simultáneamente en un envase primario adecuado. Los ingredientes activos están presentes en el envase primario en cada caso en recipientes separados que pueden ser, por ejemplo, tubos, frascos o blísteres. Este envase separado de los componentes en el envase primario conjunto es también denominado un kit.

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En una realización, las composiciones farmacéuticas de la presente invención se pueden combinar con otros agentes oftalmológicos. Los ejemplos de tales agentes incluyen pero no se limitan a carotenoides como licopeno, luteína, zeaxantina, fitoeno, fitoflueno, ácido carnósico y derivados de los mismos como carnosol, ácido 6,7-deshidrocarnósico, ácido 7-cetocarnósico, una fuente de zinc como óxido de zinc o una sal de zinc como su sal de cloruro, acetato, gluconato, carbonato, sulfato, borato, nitrato o silicato, óxido de cobre, vitamina A, vitamina C, vitamina E y/o β -caroteno.

En otra realización, las composiciones farmacéuticas de la presente invención se pueden combinar con otras quinasas de receptores dirigidos a inhibidores de la transducción de señales de las familias de dominios de, por ejemplo VEGFR, PDGFR, FGFR y sus ligandos respectivos u otros inhibidores de rutas como VEGF-Trap (aflibercept), pegaptanib, ranibizumab, pazopanib, bevasiranib, KH-902, mecamilamina, PF-04523655, E-10030, ACU-4429, volociximab, sirolimus, fenretinide, disulfiram, sonenpcizumab y/o tandospirona. Estos agentes incluyen, sin carácter limitante, anticuerpos como Avastina (bevacizumab). Estos agentes también incluyen, sin carácter limitante, inhibidores de moléculas pequeñas como STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al.,

Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539), PKC412, nepafenac.

Se da preferencia a una combinación con bevacizumab, aflibercept, pegaptanib, ranibizumab pazopanib, y/o bevasiranib.

5 Generalmente, el uso de los otros agentes oftalmológicos en combinación con las composiciones farmacéuticas de la presente invención servirá para:

(1) obtener una mejor eficacia en comparación con la administración de cada medicamento por separado,

10 (2) proporcionar la administración de cantidades menores de los medicamentos administrados,

(3) proporcionar el tratamiento de un espectro más amplio de mamíferos, especialmente seres humanos,

(4) proporcionar una mayor tasa de respuesta entre los pacientes tratados,

15 (5) obtener resultados de eficacia y tolerabilidad al menos tan buenos como los de los agentes usados solos, en comparación con casos conocidos en los que otras combinaciones de agentes producen efectos antagonistas. Se considera que el experto en la técnica, utilizando la información anterior y la información disponible en la técnica, puede utilizar la presente invención en
20 toda su extensión.

Será evidente para un experto en la técnica que se pueden hacer cambios y modificaciones en esta invención sin apartarse del espíritu o alcance de la misma como se establece en el presente documento.

25 Todas las publicaciones, solicitudes y patentes citadas anteriormente y a continuación se incorporan al presente documento por referencia.

Los datos de peso son, a menos que se indique lo contrario, porcentajes en peso y las partes son partes en peso.

Ejemplos:

Procedimientos de HPLC:

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Se desarrollaron dos procedimientos de HPLC distintos para la determinación del contenido de regorafenib, productos de degradación no identificados y componentes secundarios no identificados, así como para la determinación del producto de degradación específico metilamida del ácido 4-
5 (4-amino-3-fluorofenoxi)piridin-2-carboxílico (AFP-PMA), respectivamente, en las formulaciones farmacéuticas.

1) Procedimiento de HPLC para la determinación del contenido de regorafenib, componentes secundarios no identificados, y productos de degradación no identificados: Las muestras se prepararon por dilución de
10 alícuotas de la formulación extraídas con agua/acetonitrilo (25/75) a una concentración final de regorafenib de 100 µg/ml. Se inyectaron 10 µl de cada muestra en un sistema de HPLC Agilent 1100 (Agilent, Waldbronn, Alemania), y las muestras se procesaron en una columna de C18 Symmetry (150 x 4,6 mm -
3,5 µm de tamaño de partícula, Waters, Eschborn, Alemania) calentada (40 °C)
15 aplicando un caudal de 1ml/min. La fase móvil consistía de una mezcla de tampón de fosfato potásico pH 2,4 (A) y acetonitrilo/etanol (4.6) (B). Se aplicó el siguiente gradiente: 0 minutos: A, 60% / B, 40%; 12 minutos: A, 20% / B, 80%;
16 minutos: A, 20% / B, 80%; 16,5 minutos: A, 60% / B, 40%; 20 minutos: A, 60% / B, 40%. El regorafenib, los componentes secundarios no identificados y
20 los productos de degradación no identificados fueron cuantificados usando un detector DAD a una longitud de onda de 265 nm. El contenido de regorafenib (columna 3 en las tablas a continuación) en las formulaciones se cuantificó mediante el uso de una recta de calibración de 2 puntos externa. Los componentes secundarios no identificados y los productos de degradación no
25 identificados (columnas 5-7 en las tablas a continuación) se describen como % de las áreas de picos relacionados con la muestra resumidas. La precisión del sistema se determinó con cada grupo de muestras procesado, mediante una inyección repetida seis veces de un patrón de regorafenib 100% (por ejemplo, 100 µg/ml), el coeficiente de variación de las áreas de los picos resultantes de

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estas seis inyecciones estuvo siempre por debajo del 2%. La ordenada en el origen relativa al eje Y de una recta de calibración de dos puntos (por ejemplo, 50 µg/ml, 100 µg/ml) estuvo siempre por debajo del 3% (con referencia al estándar de regorafenib 100%). El pico de regorafenib aparece a los 11,5 minutos.

Alternativamente (ejemplos 3 a 5), el contenido de regorafenib y sus productos de degradación se determina por un procedimiento de HPLC diferente pero similar, utilizando columnas de fase inversa de 100 mm x 4,6 mm (YMC Pack Pro C18 RS, 3 µm de tamaño de partícula). Se inyectaron muestras de 5 µl con un contenido nominal de 0,16 mg/ml y se eluyeron con un gradiente de fase móvil que consistía en ácido trifluoroacético (2 ml por litro de agua) (A) y acetonitrilo (B) a un caudal de 1,0 ml/min. Se aplicaron las siguientes condiciones de gradiente: 0 - 1 min 75% A / 25 % B; hasta los 3,5 min en que se cambió a 50 % A / 50 % B; hasta los 11,5 min en que se cambió a 43 % A / 57 % B; hasta los 13 min en que se cambió a 15 % A / 85 % B y se mantuvo hasta los 16 min a 15 % A / 85 % B, seguido por re-equilibrio a 75% A / 25 % B. La temperatura de la columna era de 40 °C y la longitud de onda de detección era de 260 nm (usando detección con disposición de diodos). La cuantificación de regorafenib se realizó a través de un estándar externo con calibración de 3 puntos. Los productos de degradación se cuantifican usando la misma función de calibración obtenida con el estándar de referencia de regorafenib. Este procedimiento de HPLC está totalmente validado para una dosificación oral sólida que contiene regorafenib y cumple todos los requerimientos con respecto a selectividad, precisión, linealidad y robustez. El tiempo de elución del pico de regorafenib es aproximadamente el mismo que para el procedimiento descrito anteriormente

2) Procedimiento de HPLC para la determinación del producto de degradación específico metilamida del ácido 4-(4-amino-3-fluorofenoxi)piridin-2-carboxílico (IUPAC: 4-(4-amino-3-fluorofenoxi)-N-metilpiridina-2-carboxamida)

(AFP-PMA). Las muestras se prepararon por dilución de alícuotas de formulación extraídas con acetona a una concentración final de regorafenib de 3000 µg/ml. Se inyectaron 15µl de cada muestra en un sistema de HPLC Agilent 1100 (Agilent, Waldbronn, Alemania), y las muestras mantenidas a 10°

5 en el inyector automático se procesaron en una columna de C18 Symmetry (150 x 4,6 mm - 3,5 µm de tamaño de partícula, Waters, Eschborn, Alemania) mantenida a 20 °C con un caudal de 1ml/min. La fase móvil consistía en una mezcla de tampón de fosfato potásico pH 2,4 (A) y acetonitrilo/etanol (6/4) (B). Se aplicó el siguiente gradiente: 0 minutos: A, 62% / B, 38%; 5 minutos: A, 44%

10 / B, 56%; 5,01 minutos: A, 15% / B, 85%; 9 minutos: A, 15% / B, 85%; 9,01 minutos: A, 62% / B, 38%; 12 minutos: A, 62% / B, 38%. La metilamida del ácido 4-(4-amino-3-fluorofenoxi)piridin-2-carboxílico (columna 4 en las tablas a continuación) se cuantificó utilizando un detector de DAD a una longitud de onda de 232 nm, refiriéndose a una recta de calibración de 3 puntos externa

15 (por ejemplo 0,04 µg/ml, 0,1 µg/ml, 1 µg/ml). El pico de la metilamida del ácido 4-(4-amino-3-fluorofenoxi)piridin-2-carboxílico de ácido metilamida aparece a los 3,9 minutos. El límite de detección (LOD) y el límite de cuantificación (LDC) de la metilamida del ácido 4-(4-amino-3-fluorofenoxi)piridin-2-carboxílico se determinaron para dos matrices diferentes (agua y parafina), y eran: LOD: 4

20 ppm = 0,0004% (agua), 13 ppm = 0,0013% (parafina), LDC: 13 ppm = 0,0013% (agua) y 43 ppm = 0,0043% (parafina).

Ejemplo 1: Suspensión oftalmológica que comprende monohidrato de regorafenib en glicérido de oleoil polietilenglicol (20 mg/ml)

Se suspendieron 200 mg de monohidrato de regorafenib micronizado en

25 glicérido de oleoil polietilenglicol (10 ml). La suspensión se homogeneizó por agitación a temperatura ambiente durante 15 minutos.

La estabilidad de regorafenib en glicérido de oleoil polietilenglicol se probó a una concentración de 3 mg/ml durante 4 semanas a 25 °C, 60% de humedad relativa (HR) y 40 °C, 75% HR. El contenido de regorafenib varió

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entre 95,0-101% de la concentración teórica, el mayor producto de degradación no identificado varió de 0,3 a 0,7%. El contenido de metilamida del ácido 4-(4-amino-3-fluorofenoxi)piridin-2-carboxílico (AFP-PMA) estuvo por debajo de <13 ppm = 0,0013% (< LOD determinado para una formulación a base de parafina en la Tabla 2). Para detalles analíticos véase la sección Procedimiento de HPLC anterior.

Tabla 2. Contenido y estabilidad de regorafenib en una formulación basada en glicérido de oleoil polietilenglicol:

1	2	3	4	5	6	7
Tiempo de almacenamiento	Condición de almacenamiento	Contenido de regorafenib (% del valor teórico), mediante	Contenido de AFP-PMA (% con referencia a regorafenib), mediante	Componente secundario no identificado mayor en el patrón (% de	Componente secundario no identificado mayor en la muestra (% de	Producto de degradación no identificado mayor en la muestra (% de

10 (continuación)

		calibración externa	calibración externa	áreas de pico resumidas)	de áreas de pico resumidas)	de áreas de pico resumidas)
0		95,0	< 0,0013	0,04	0,04	0,7
1 día	25°C/ 60% H.R.	101	< 0,0013	0,04	0,04	0,6
4 semanas	25°C/ 60% H.R.	99,0	< 0,0013	0,04	0,04	0,3
4 semanas	40°C/ 75% H.R.	98,7	< 0,0013	0,04	0,04	0,3

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Ejemplo 2: Suspensión oftalmológica que comprende monohidrato de regorafenib en parafina líquida (20 mg/ml)

Se suspendieron 400 mg de monohidrato de regorafenib micronizado en 20 ml de parafina líquida liviana. La suspensión se homogeneizó por agitación a temperatura ambiente durante 15 minutos.

La estabilidad de la suspensión se probó a una concentración de 20mg/ml durante 13 semanas a 25 °C, 60% de humedad relativa (HR) y 40 °C, 75% HR. El contenido de regorafenib varió entre 74,8-99,6% de la concentración teórica. La fluctuación observada se debe muy probablemente a falta de homogeneidad de la muestra después de la agitación manual de la suspensión. No se observó ningún producto de degradación no identificado en los cromatogramas. El contenido de AFP-PMA estaba por debajo de <43 ppm = 0,0043% (< LOQ determinado para una formulación basada en parafina, Tabla 3). Para detalles analíticos véase la sección Análisis anterior.

Tabla 3. Contenido y estabilidad de regorafenib en una formulación basada en parafina.

1	2	3	4	5	6	7
Tiempo de almacena- miento	Condición de almacena- miento	Contenido de regorafenib (% del valor teórico), mediante calibración externa	Contenido de AFP-PMA (% con referencia a regorafenib), mediante calibración externa	Componente secundario no identificado mayor en el patrón (% de áreas de pico resumidas)	Componente secundario no identificado mayor en la muestra (% de áreas de pico resumidas)	Producto de degradación no identificado mayor en la muestra (% de áreas de pico resumidas)
0		99,6	< 0,0043	0,04	0,04	-
4 semanas	25°C / 60% HR	85,4	< 0,0043	0,04	0,04	-

4 semanas	40°C / 75% HR	74,8	< 0,0043	0,04	0,04	-
13 semanas	25°C / 60% HR	96,9	< 0,0043	0,04	0,04	-
13 semanas	40°C / 75% HR	94,6	< 0,0043	0,04	0,04	-

Ejemplo 3: Suspensión oftalmológica que comprende monohidrato de regorafenib y sílice coloidal hidrófoba 0,5% en parafina líquida (20 mg/ml)

Se dispersaron 0,25 g de sílice coloidal hidrófoba (Aerosil® R972) en parafina líquida liviana (50 ml) por agitación a temperatura ambiente para preparar el vehículo de suspensión (sílice coloidal hidrófoba 0,5% (p/v) en parafina líquida liviana). Se añadieron 200 mg de monohidrato de regorafenib a una alícuota del vehículo de suspensión (10 ml) y la suspensión se homogeneizó durante 45 min. usando un molino de vibración a una frecuencia de 9,1 seg⁻¹.

Posteriormente, la suspensión se introdujo en viales de vidrio (aproximadamente 6 ml por vial) y los viales se cerraron con tapones de caucho y se encapsularon con tapas de aluminio de precisión.

La estabilidad de la suspensión se probó durante 4 semanas a 4 °C, temperatura ambiente (aprox. 25 °C) y 40 °C / 75% de humedad relativa (véase la Tabla 4). La variación y las concentraciones aparentes más altas en relación con el contenido nominal (entre 100 y 125%) se deben muy probablemente a un artefacto en la preparación de las muestras para el análisis. El modo de preparación de la muestra de suspensiones que contenían sílice ha sido optimizado posteriormente como se describe en el ejemplo 4 b).

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Tabla 4. Contenido y estabilidad de regorafenib en la formulación del Ejemplo 3

Condición de almacenamiento	Contenido de regorafenib ¹ (g/l)	Contenido de regorafenib (% del valor nominal)	Producto de degradación/ máx., individual (%)	Contenido de AFP-PMA (%)	Productos de degradación/ suma (%)
4°C	21,07	109,3	0,05	<0,005	0,05
TA	24,13	125,2	0,05	<0,005	0,05
40°C/ 75 % HR	19,41	100,7	<0,05	<0,005	<0,05

5 ¹ en base al principio activo anhidro

Ejemplo 4: Suspensión oftalmológica que comprende monohidrato de regorafenib y sílice coloidal hidrófoba 2% en parafina líquida (20 mg/ml)

a)

10 Se dispersó 1 g de sílice coloidal hidrófoba (Aerosil® R972) en parafina líquida liviana (50 ml) por agitación a temperatura ambiente para preparar el vehículo de suspensión (sílice coloidal hidrófoba 2% (p/v) en parafina líquida liviana). Se añadieron 200 mg de monohidrato de regorafenib a una alícuota del vehículo de suspensión (10 ml) y la suspensión se homogeneizó durante 45
15 min. usando un molino de vibración a una frecuencia de 9,1 seg⁻¹.

Posteriormente, la suspensión se introdujo en viales de vidrio (aproximadamente 6 ml por vial) y los viales se cerraron con tapones de caucho y se sellaron con tapas de aluminio crimpadas.

20 La estabilidad de la suspensión se probó durante 4 semanas a 4 °C, temperatura ambiente (aprox. 25 °C) y 40 °C / 75% de humedad relativa (véase

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la Tabla 5). La variación y las concentraciones aparentes más altas en relación con el contenido nominal (entre 104 y 118%) se deben muy probablemente a un artefacto en la preparación de las muestras para el análisis. El modo de preparación de la muestra de suspensiones que contenían sílice ha sido optimizado posteriormente como se describe en el ejemplo 4 b).

Tabla 5. Contenido y estabilidad de regorafenib en la formulación del Ejemplo 4a)

Condición de almacenamiento	Contenido de regorafenib ¹ (g/l)	Contenido de regorafenib (% del valor nominal)	Producto de degradación/ máx. individual (%)	Contenido de AFP-PMA (%)	Productos de degradación/ suma (%)
4°C	20,01	103,8	<0,05	<0,005	<0,05
TA	21,84	113,3	0,05	<0,005	0,05
40°C/ 75 % HR	22,67	117,6	0,05	<0,005	0,05

¹ en base al principio activo anhidro

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b)

Se dispersaron 10 g de sílice coloidal hidrófoba (Aerosil® R972) en parafina líquida liviana (500 ml) por agitación a temperatura ambiente durante 15 minutos usando un mezclador de alta cizalladura (10230 rpm) para preparar el vehículo de suspensión (sílice coloidal hidrófoba 2% (p/v) en parafina líquida liviana). Se añadieron 9 g de monohidrato de regorafenib a una alícuota del vehículo de suspensión (450 ml) y la suspensión se homogeneizó durante 45 min. usando un mezclador de alta cizalladura (10230 rpm).

La suspensión se introdujo en viales de vidrio (5 ml por vial) y los viales se cerraron con tapones de caucho y se encapsularon con tapas de aluminio de

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presión. Posteriormente, los viales se irradiaron por radiación gamma a una dosis efectiva de 27,9 kGy.

La estabilidad de la suspensión irradiada se probó durante 4 semanas a 40 °C/75% de humedad relativa (véase Tabla 6). El modo de preparación de las suspensiones que contenían sílice se optimizó en este punto de tiempo. El contenido de regorafenib varió entre 98 y 103% del contenido nominal. El contenido de AFP-PMA estaba por debajo de 0,005% (50 ppm).

Tabla 6. Contenido y estabilidad de regorafenib en la formulación del Ejemplo 4 b)

Tiempo de almacenamiento	Radiación gamma (27,9 kGy)	Condición de almacenamiento	Contenido de regorafenib ¹ (g/l)	Contenido de regorafenib (% del valor nominal)	Producto de degradación / máx. individual (%)	Contenido de AFP-PMA (%)	Productos de degradación / suma (%)
0	No	-	19,51	101,2	0,05	<0,005	0,05
0	Sí	-	18,96	98,3	0,05	<0,005	0,05

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(continuación)

4	Sí	40°C/75 % HR	19,74	102,4	0,05	<0,005	0,1
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¹ en base al principio activo anhidro

Ejemplo 5: Suspensión oftalmológica que comprende monohidrato de regorafenib y sílice coloidal hidrófoba 5% en parafina líquida (20 mg/ml)

Se dispersaron 2,5 g de sílice coloidal hidrófoba (Aerosil® R972) en parafina líquida liviana (50 ml) por agitación a temperatura ambiente para preparar el vehículo de suspensión (sílice coloidal hidrófoba 5% (p/v) en parafina líquida liviana). Se añadieron 200 mg de monohidrato de regorafenib a una alícuota del vehículo de suspensión (10 ml) y la suspensión se

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homogeneizó durante 45 min. usando un molino de vibración a una frecuencia de 9,1 seg⁻¹.

Posteriormente, la suspensión se introdujo en viales de vidrio (aproximadamente 6 ml por vial) y los viales se cerraron con tapones de caucho y se encapsularon con tapas de aluminio de presión.

La estabilidad de la suspensión se probó durante 4 semanas a 4 °C, temperatura ambiente (aprox. 25 °C) y 40 °C / 75% de humedad relativa (véase la Tabla 7). La variación en el contenido (entre 99 y 97%) se debe muy probablemente a un artefacto en la preparación de las muestras para el análisis.

El modo de preparación de la muestra de suspensiones que contenían sílice ha sido optimizado posteriormente como se describe en el ejemplo 4 b).

Tabla 7. Contenido y estabilidad de regorafenib en la formulación del Ejemplo 5

Condición de almacena miento	Contenido de regorafenib ¹ (g/l)	Contenido de regorafenib (% del valor nominal)	Producto de degradación / máx. individual (%)	Contenido de AFP-PMA (%)	Productos de degradación / suma (%)
4°C	19,14	99,3	<0,05	<0,005	<0,05
TA	18,55	96,2	<0,05	<0,005	<0,05
40°C/ 75 % HR	18,76	97,3	<0,05	<0,005	<0,05

¹ en base al principio activo anhidro

Ejemplo 6: Suspensión oftalmológica que comprende monohidrato de regorafenib en un vehículo basado en agua (20 mg/ml)

Se dispersaron 1,7 g de hidroxipropilmetilcelulosa 15 cp (HPMC) en una solución isotónica de cloruro sódico (48 g, 0,9% de NaCl en agua) a 70 °C. La mezcla se enfrió a temperatura ambiente mientras se agitaba. Se evaporó el agua a temperatura ambiente y, posteriormente, se añadió polisorbato 80 (0,5

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- g) y se disolvió bajo agitación moderada. Se añadieron 518 mg de monohidrato de regorafenib a una alícuota del vehículo preparado (24,5 g) y la suspensión se homogeneizó por agitación suave a temperatura ambiente durante 15 minutos.
- 5 La estabilidad de la suspensión se probó a una concentración de 10 mg/ml durante 13 semanas a 25 °C, 60% de humedad relativa (HR) y 40 °C, 75% HR. El contenido de regorafenib varió entre 103-112% de la concentración teórica. La fluctuación observada se debe muy probablemente a la falta de homogeneidad de la muestra después de la agitación manual de la suspensión.
- 10 El mayor producto de degradación no identificado era <0,1% de las áreas de pico relacionadas con la muestra resumidas. La cantidad de AFP-PMA se determinó sólo después de 9 semanas de almacenamiento.

15 Tabla 8. Contenido y estabilidad de regorafenib en una formulación basada en agua.

1	2	3	4	5	6	7
Tiempo de almacena- miento	Condición de almacena- miento	Contenido de regorafenib (% del valor teórico), mediante calibración externa	Contenido de AFP-PMA (% con referencia a regorafenib), mediante calibración externa	Componente secundario no identificado mayor en el patrón (% de áreas de pico resumidas)	Componente secundario no identificado mayor en la muestra (% de áreas de pico resumidas)	Producto de degradación no identificado mayor en la muestra (% de áreas de pico resumidas)
0		103	n,d,	0,04	0,04	-
4 semanas	25°C/60% HR	104	n,d,	0,1	0,04	-
4 semanas	40°C/75%	112	n,d,	0,1	0,04	-

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B

	HR					
9 semanas	25°C/60%		0,0056			
	HR					

(continuación)

9 semanas	40°C/75%		0,0086			
	HR					
13 semanas	25°C/60%	104	n,d,	0,06	0,04	-
	HR					
13 semanas	40°C/75%	104	n,d,	0,06	0,04	-
	HR					

En las tablas 2, 3 y 8 anteriores la columna 5 describe la cantidad porcentual del mayor componente secundario no identificado en el estándar usado en el procedimiento de HPLC para ser comparado con el valor de la columna 6 que describe la cantidad porcentual del mismo componente secundario no identificado en la formulación. La columna 7 describe la cantidad porcentual del mayor producto de degradación no identificado en la formulación que no es AFP-PMA. Dicho producto de degradación no es detectable en el patrón sino que se forma en la formulación.

Ejemplo 7: Suspensión oftalmológica que comprende monohidrato de regorafenib en triglicéridos de cadena media (MCT, migliol) (20 mg/ml)

El ejemplo 7 se preparó de acuerdo con el ejemplo 1.

Tabla 9. Contenido y estabilidad de regorafenib en una formulación en base a MCT.

1	2	3	4	5	6	7
Tiempo	Condición	Contenido de	Contenido de	Componente	Componente	Producto de

ug
m

de almacena- miento	de almacena- miento	regorafenib (%) del valor teórico), mediante calibración externa	AFP-PMA (%) con referencia a regorafenib), mediante calibración externa	secundario no identificado mayor en el patrón (% de áreas de pico resumidas)	secundario no identificado mayor en la muestra (% de áreas de pico resumidas)	degradación no identificado mayor en la muestra (% de áreas de pico resumidas)
0		106,0	<0,0043	<0,1	<0,1	<0,1
4 semanas	25°C/60% HR	99,5	<0,0043	<0,1	<0,1	<0,1
4 semanas	40°C/75% HR	101,8	<0,0043	<0,1	<0,1	<0,1
13 semanas	25°C/60% HR	101,0	<0,0043	<0,1	<0,1	<0,1
13 semanas	40°C/75% HR	101,5	<0,0043	<0,1	<0,1	<0,1

Ejemplo 8: Suspensión oftalmológica que comprende monohidrato de regorafenib en oculentum simple (20 mg/g)

Se suspendieron 100 mg de monohidrato de regorafenib micronizado en 4900 mg de oculentum simple (composición: colesterol 1%, parafina líquida 42,5%, parafina blanda 56,5% en peso). La suspensión se homogeneizó por agitación a temperatura ambiente en un mortero de ágata durante aproximadamente 1 minuto.

Ejemplo 9: Eficacia tópica de diferentes formulaciones que contienen regorafenib en un modelo de neovascularización coroidea (CNV) inducida por láser

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El objetivo de este estudio era determinar si la administración tópica dos veces al día (gotas oculares) de las composiciones farmacéuticas oftalmológicas tópicas de acuerdo con la invención resultan en una disminución de la pérdida vascular y/o neovascularización coroidea en un modelo de rata de neovascularización coroidea inducida por láser (Dobi et al, Arch. Ophthalmol. 1989, 107 (2), 264-269 o Frank et al, Curr. Eye Res. Mar 1989, 8 (3), 239-247).

Para este propósito, se seleccionaron un total de 133 de ratas Brown-Norway pigmentadas sin ningún signo visible de defectos oculares y se asignaron aleatoriamente a ocho grupos de seis a ocho animales cada uno. En el día 0, los animales se anestesiaron mediante una inyección intraperitoneal (15 mg/kg de xilazina y 80 mg/kg de ketamina (disueltos en agua que contenía 5 mg/ml de hemihidrato de clorobutanol y propilenglicol). Después de la instilación de una gota de atropina al 0,5% (disuelta en solución salina al 0,9% que contenía cloruro de benzalconio) para dilatar las pupilas, se indujo la neovascularización coroidea quemando seis orificios en la retina (ruptura de la membrana de Bruch) de un ojo por animal (tamaño de la lesión: 50 μ m, intensidad del láser: 150 mW; duración del estímulo: 100 msec), usando un láser de argón de 532 nm.

Se incluyeron las siguientes formulaciones:

- a) Glicéridos de oleoil polietilenglicol al 100% como se utilizan en el ejemplo 1 (control de vehículo), n = 8
- b) Ejemplo 1 (20 mg/ml, suspensión), n = 8
- c) Parafina líquida liviana al 100% como se utiliza en el ejemplo 2 (control de vehículo), n = 8
- d) Ejemplo 2 (20 mg/ml, suspensión), n = 8
- e) Vehículo basado en agua (3,5% de Hidroxipropilmetilcelulosa 15 cp, 0,5% de polisorbato 80, 96% de solución isotónica de NaCl como se usa en el ejemplo 6 (control de vehículo), n = 6

- f) Ejemplo 6 (20 mg/ml, suspensión), n = 6
- g) Sílice coloidal hidrófoba al 0,5% en parafina líquida como se usa en el ejemplo 3 (control de vehículo), n = 10
- h) Ejemplo 3 (20 mg/ml, suspensión), n = 10
- 5 i) Sílice coloidal hidrófoba al 2,0% en parafina líquida como se usa en el ejemplo 4 (control de vehículo), n = 10
- j) Ejemplo 4 (20 mg/ml, suspensión), n = 10
- k) Sílice coloidal hidrófoba al 5,0% en parafina líquida como se usa en el ejemplo 5 (control de vehículo), n = 10
- 10 l) Ejemplo 5 (20 mg/ml, suspensión), n = 10
- m) Migliol al 100 % como se usa en el ejemplo 7 (control de vehículo), n = 8
- n) Ejemplo 7 (20 mg/ml, suspensión), n = 7
- o) Oculentum simple al 100% como se usa en el ejemplo 8
- 15 (control de vehículo), n = 8
- p) Ejemplo 8 (20 mg/g, suspensión), n = 6

De cada formulación, se aplicaron 10 µl en el ojo afectado dos veces al día a un intervalo de 10:14 horas durante el período de observación completa de 23 días. El peso corporal de todos los animales se registró antes del inicio y una vez al día durante el estudio. Se realizó una angiografía en el día 21 usando una cámara de fondo de fluorescencia (Kowe Genesis Df, Japón). Aquí, después de la anestesia y la dilatación pupilar, se inyectó por vía subcutánea fluoresceína sódica 10% (colorante, disuelta en agua) y se registraron imágenes aproximadamente 2 minutos después de la inyección del colorante. La pérdida vascular de la fluoresceína en los angiogramas se evaluó por tres examinadores diferentes que fueron cegados para la asignación del grupo (ejemplos 1 a 3 versus respectivo vehículo). Cada lesión se calificó con 0 (sin pérdidas) a 3 (fuertemente teñido), y se usó una media de las 6 lesiones como el valor para el animal respectivo. En el día 23, los animales se sacrificaron y

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los ojos se recolectaron y fijaron en solución de paraformaldehído 4% durante 1 hora a temperatura ambiente. Después del lavado, la retina se desprendió cuidadosamente, y el complejo esclerótica-coroides se lavó, bloqueó y tiñó con un anticuerpo FITC-isolectina B4 con el fin de visualizar la vasculatura. A 5 continuación, la esclerótica-coroides se montó en plano y se examinó bajo un microscopio de fluorescencia (Keyence Biozero) a una longitud de onda de excitación de 488 nm. El área (en μm^2) de neovascularización coroidea se midió usando el software ImageTool.

Resultados:

10 A) Eficacia en relación con la pérdida vascular (puntuaciones de angiografía día 21):

Fig. 1: Puntuaciones de angiografía de animales tratados con vehículo (glicéridos de oleoil polietilenglicol (Labrafil), formulación a) y regorafenib (ejemplo 1, formulación b) en el día 21. Los datos se presentan como media $\pm$ 15 SD, valor de p según la prueba t. N = 8 por grupo.

Tabla 10: Datos en bruto del histograma mostrado en la Fig. 1. Los valores individuales representan las medias a partir de tres observadores diferentes cegados con respecto al tratamiento.

Animal	Glicéridos de oleil polietilenglicol 100% (formulación a)	Ejemplo 1 (formulación b)
1	1,80	1,14
2	1,72	0,67
3	1,63	1,44
4	1,72	0,90
5	1,67	1,00
6	2,00	1,22
7	1,56	1,33
8	2,33	1,33

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Fig. 2: Puntuaciones de angiografía de animales tratados con vehículo (parafina, formulación c) y regorafenib (ejemplo 2, formulación d) en el día 21. Los datos se presentan como media $\pm$ SD, valor de p según la prueba t. N = 8 por grupo.

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Tabla 11: Datos en bruto del histograma mostrado en la Fig. 2. Los valores individuales representan las medias a partir de tres observadores diferentes cegados con respecto al tratamiento.

Animal	Parafina 100% (formulación c)	Ejemplo 2 (formulación d)
1	2,33	1,29
2	1,77	1,78
3	1,50	0,69
4	1,91	1,34
5	2,21	0,67
6	2,06	1,00
7	2,10	0,96
8	2,54	1,51

5 Fig. 3: Puntuaciones de angiografía de animales tratados con vehículo (a base de agua, formulación e) y regorafenib (ejemplo 3, formulación f) en el día 21. Los datos se presentan como media $\pm$ SD, valor de p según la prueba t. N = 6 por grupo.

10 Tabla 12: Datos en bruto del histograma mostrado en la Fig. 3. Los valores individuales representan las medias a partir de tres observadores diferentes cegados con respecto al tratamiento.

Animal	Formulación e	Ejemplo 3 (formulación f)
1	1,61	1,78
2	1,78	1,60
3	1,93	1,34

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(continuación)

Animal	Formulación e	Ejemplo 3 (formulación f)
4	2,27	2,00
5	1,49	0,80
6	2,10	2,20

B) Eficacia en relación con la neovascularización (área neovascular día 23):

5 Fig. 4: Área neovascular de animales tratados con vehículo (glicéridos de oleoil polietilenglicol (Labrafil), formulación a) y regorafenib (ejemplo 1, formulación b) en el día 23. Los datos se presentan como media $\pm$ SD, valor de p según la prueba t. N = 8 por grupo.

10 Tabla 13: Datos en bruto del histograma mostrado en la Fig. 4. Los valores individuales representan las medias de las seis lesiones.

Animal	Glicéridos de oleoil polietilenglicol 100% (formulación a)	Ejemplo 1 (formulación b)
1	134507	90562
2	70878	59819
3	84254	67222
4	86071	72584
5	93586	30455
6	69696	47866
7	103307	23991
8	98472	63033

Fig. 5: Área neovascular de animales tratados con vehículo (parafina, formulación c) y regorafenib (ejemplo 2, formulación d) en el día 23. Los datos se presentan como media $\pm$ SD, valor de p según la prueba t. N = 8 por grupo.

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Tabla 14: Datos en bruto del histograma mostrado en la Fig. 5. Los valores individuales representan las medias de las seis lesiones.

Animal	Parafina 100 % (formulación c)	Ejemplo 2 (formulación d)
1	105910	62047
2	81060	70927
3	98735	84481
4	85019	80151
5	98071	70568
6	101668	59804
7	99413	63145
8	113797	91466

Fig. 6: Área neovascular de animales tratados con vehículo (a base de agua, formulación e)) y regorafenib (ejemplo 3, formulación f) en el día 23. Los datos se presentan como media $\pm$ SD, valor de p según la prueba t. N = 5 por grupo.

Tabla 15: Datos en bruto del histograma mostrado en la Fig. 6. Los valores individuales representan las medias de las seis lesiones.

Animal	Formulación e	Ejemplo 3 (formulación f)
1	78759	107547
2	83420	117379
3	96239	72404
4	107654	99371
5	87960	91977

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En ambos grupos, no se pudo calificar una preparación montada en plano debido a la mala calidad de los tejidos

Resultados para el ejemplo 1:

Tabla 16 (n = 8 por grupo)

Formulación	A) Pérdida vascular [puntuación de angiografía]	B) Tamaño de la lesión de neovascularización coroidea [μm^2]
a) Glicéridos de oleil polietilenglicol 100% (control de vehículo)	1,80 $\pm$ 0,25	92596 $\pm$ 20754
b) Regorafenib (20 mg/ml) suspensión en glicéridos de oleil polietilenglicol 100% (Ejemplo 1)	1,13 $\pm$ 0,26	56942 $\pm$ 22025
valor p	< 0,001	0,005

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Resultados para el ejemplo 2:

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Tabla 17 (n = 8 por grupo)

Formulación	A) Pérdida vascular [puntuación de angiografía]	B) Tamaño de la lesión de neovascularización coroidea [μm^2]
c) Parafina líquida 100% (control de vehículo)	2,05 ± 0,33	97959 ± 10580
d) Regorafenib (20 mg/ml) suspensión en parafina líquida 100 % (ejemplo 2)	1,16 ± 0,39	72824 ± 11496
valor p	< 0,001	< 0,001

Resultados para el ejemplo 6:

Tabla 18 (n = 6 por grupo para pérdida, n = 5 por grupo para neovascularización)

Formulación	A) Pérdida vascular [puntuación de angiografía]	B) Tamaño de la lesión de neovascularización coroidea [μm^2]
e) Control de vehículo basado en agua	1,86 ± 0,30	90806 ± 11414
f) Regorafenib (20 mg/ml) suspensión en vehículo basado en agua (ejemplo 6)	1,62 ± 0,50	97736 ± 17027
valor p	0,330 (n.s.)	0,471 (n.s.)

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Resultados para el ejemplo 7:

Tabla 19 (n = 8 para vehículo, n = 7 para regorafenib)

Formulación	A) Pérdida vascular [puntuación de angiografía]	B) Tamaño de la lesión de neovascularización coroidea [μm^2]
m) Triglicéridos de cadena media 100% (Migliol, control de vehículo)	1,53 $\pm$ 0,50	84971 $\pm$ 14882
n) Regorafenib (20 mg/ml) suspensión en migliol	1,40 $\pm$ 0,27	68127 $\pm$ 8954
valor p	0,567 (n.s.)	0,022

Resultados para el ejemplo 8:

5 Tabla 20 (n = 8 para vehículo, n = 6 para regorafenib)

Formulación	A) Pérdida vascular [puntuación de angiografía]	B) Tamaño de la lesión de neovascularización coroidea [μm^2]
o) 100% Oculentum simple (control de vehículo)	1,41 $\pm$ 0,41	83301 $\pm$ 9729
p) Regorafenib (20 mg/g) suspensión en oculentum simple	1,11 $\pm$ 0,36	60628 $\pm$ 17812
valor p	0,180 (n.s.)	0,010

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Resultados para el ejemplo 3, 4 y el ejemplo 5:

Tabla 21 (n = 8 a 10 por grupo)

Formulación	A) Pérdida vascular [puntuación de angiografía]	B) Tamaño de la lesión de neovascularización corioidea [μm^2]
g) Aerosil 0,5% en parafina líquida (control de vehículo), n=10	1,65 $\pm$ 0,15	78040 $\pm$ 21180
h) Regorafenib (20 mg/ml) suspensión de Aerosil 0,5% en parafina líquida (ejemplo 3), n=9 para A), n=10 para B)	1,14 $\pm$ 0,34	55364 $\pm$ 8307
i) Aerosil 2% en parafina líquida (control de vehículo), n=10	1,63 $\pm$ 0,16	82750 $\pm$ 12471
j) Regorafenib (20 mg/ml) suspensión de Aerosil 2% en parafina líquida (ejemplo 4), n=8 para A), n=10 para B)	1,11 $\pm$ 0,13	51209 $\pm$ 4463
k) Aerosil 5% en parafina líquida (control de vehículo)	1,70 $\pm$ 0,24	66389 $\pm$ 8790

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(continuación)

l) Regorafenib (20 mg/ml) suspensión de Aerosil 5% en parafina líquida (ejemplo 5)	1,32 ± 0,19	54984 ± 9973
valor p g vs. h	< 0,001	0,0055
valor p i vs. j	< 0,001	< 0,001
valor p k vs. l	0,001	0,014

Ejemplo 10: Farmacocinética ocular:

5 A)

En el día del experimento se aplica una dosis definida del compuesto de prueba (monohidrato de regorafenib 20 mg/ml) como suspensión en diferentes vehículos a cada ojo mediante el uso de una pipeta Eppendorf. En un período de 24 a 96 horas después de la aplicación una secuencia (8-12 puntos de tiempo) de animales se sacrificaron para obtener los ojos de los mismos (ratas). Estos ojos se lavaron en 1 ml de solución salina fisiológica al menos 2 veces y después se secaron con un papel absorbente. Para determinar la concentración total del compuesto de prueba en el ojo, este se homogeneiza en una cantidad definida de solución salina y a una alícuota del homogeneizado se añade acetronitrilo para precipitar las proteínas en la solución. Después de la centrifugación, en el sobrenadante se cuantificaron el compuesto de prueba y sus posibles productos de descomposición conocidos con procedimientos de CL/EM-EM apropiados. Si las concentraciones del compuesto de prueba o de sus posibles productos de descomposición conocidos se determinan en algunos compartimientos definidos del ojo, los ojos se diseccionan en los compartimientos correspondientes y cada compartimiento se homogeniza, manipula y mide como se describió anteriormente.

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De ese modo se determina una curva de concentración-tiempo; esta se utiliza entonces para calcular parámetros farmacocinéticos estándar a fin de evaluar la calificación de una formulación determinada (concentración máxima y semivida). Los parámetros farmacocinéticos estándar calculados del compuesto de prueba o del ingrediente farmacéutico activo liberado del mismo son:

Los parámetros farmacocinéticos con respecto a regorafenib calculados a partir de curvas de concentración ocular tiempo para dosis iguales pero con formulaciones diferentes se muestran en la tabla siguiente.

10 Tabla 22:

	C _{max} [mg/L]	AUC _{norm} [kg*h/L]	MRT [h]
Labrafilo (ejemplo 1)	1,0	23	40
Parafaina (ejemplo 2)	1,4	28	41
Agua (ejemplo 6)	1,8	5,3	28
Migliol (ejemplo 7)	1,1	12	30
Oculentum Simple (ejemplo 8)	1,7	4,8	28

B)

15 Tres conejos hembra no anestesiados se trataron con una cantidad definida (30 µl) de suspensión en parafina en el saco lagrimal inferior de cada ojo. Usando un capilar de vidrio durante un período de 60 minutos, se recolectaron varias muestras de peso controlado (n = 8) de fluido lagrimal. La determinación de la concentración del compuesto en el fluido y la evaluación de los parámetros farmacocinéticos es la misma que la descrita anteriormente.

Tabla 23:

	C _{max} [mg/L]	AUC _{norm} [kg*h/L]	MRT [h]
Parafina (ejemplo 2)	149	99	0,6

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Los resultados muestran un tiempo de residencia sorprendentemente alto del agente activo en el fluido lagrimal y en la córnea.

Aunque la invención ha sido divulgada con referencia a realizaciones específicas, es evidente que otras realizaciones y variaciones de la invención se
5 pueden concebir por otros expertos en la técnica sin apartarse del verdadero espíritu y alcance de la invención. Las reivindicaciones están destinadas a ser interpretadas para incluir todas estas realizaciones y variaciones equivalentes.

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Reivindicaciones

1. Una composición farmacéutica oftalmológica tópica que comprende regorafenib, un hidrato, solvato o sal farmacéuticamente aceptable de regorafenib, o un polimorfo del mismo como agente activo y al menos un
5 vehículo farmacéuticamente aceptable, en la que la composición es una suspensión que comprende el agente activo suspendido en el vehículo farmacéuticamente aceptable aplicable.
2. La composición farmacéutica de la reivindicación 1 que contiene monohidrato de regorafenib como agente activo.
- 10 3. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 2, en la que el agente activo está en una forma sólida.
4. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 3, en la que el agente activo está en una forma cristalina.
5. La composición farmacéutica de cualquiera de las reivindicaciones 1 a
15 4, en la que el agente activo está en una forma microcristalina.
6. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 5, en la que la concentración del agente activo en la composición farmacéutica es de 0,01 a 10% en peso de la cantidad total de la composición.
7. La composición farmacéutica de cualquiera de las reivindicaciones 1 a
20 6, en la que el vehículo farmacéuticamente aceptable se selecciona del grupo que comprende glicéridos de oleoil polietilenglicol, glicéridos de linoleoil polietilenglicol, glicéridos de lauroil polietilenglicol, parafina líquida, parafina líquida ligera, parafina blanda (vaselina), parafina dura, aceite de ricino, aceite de cacahuete, aceite de sésamo, triglicéridos de cadena media, alcoholes
25 cetilestearílicos, lanolina, glicerol, propilenglicol, polietilenglicoles (PEG) o una mezcla de los mismos, agua o una mezcla de los mismos.
8. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 7 basada en un vehículo no acuoso.

9. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 8 basada en un vehículo hidrófobo.

10. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 9, en la que el vehículo farmacéuticamente aceptable se selecciona del grupo que comprende parafina líquida, parafina líquida ligera o una mezcla de las mismas.

11. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 10 que comprende además excipientes farmacéuticamente aceptables como estabilizadores, tensioactivos, vehículos a base de polímeros como agentes gelificantes, co-disolventes orgánicos, componentes activos de pH, componentes activos osmóticos y conservantes.

12. La composición farmacéutica de la reivindicación 11, en la que el estabilizador es una sílice hidrófoba.

13. La composición farmacéutica de la reivindicación 12 que comprende sílice hidrófoba en una cantidad de 0,1% a 10% en peso de la composición total.

14. Un procedimiento para fabricar una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 1 a 13, en el que el agente activo se suspende en un vehículo farmacéuticamente aceptable aplicable opcionalmente en presencia de uno o más excipientes farmacéuticamente aceptables adicionales y la suspensión se homogeniza.

15. La composición farmacéutica de cualquiera de las reivindicaciones 1 a 13 para el uso en el tratamiento o la prevención de un trastorno oftalmológico seleccionado del grupo que comprende degeneración macular relacionada con la edad (AMD), neovascularización coroidea (CNV), membrana neovascular coroidea (CNMV), edema macular quístico (CME), membrana epirretiniana (ERM) y agujero macular, neovascularización coroidea asociada a miopía, estrías vasculares, desprendimiento de retina, retinopatía diabética, edema macular diabético (DME), cambios atróficos del epitelio pigmentario de la retina

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(RPE), cambios hipertróficos del epitelio pigmentario de la retina (RPE), oclusión venosa de la retina, oclusión de vena coroidea de la retina, edema macular, edema macular debido a oclusión venosa de la retina, retinitis pigmentaria, enfermedad de Stargardt, glaucoma, afecciones inflamatorias, cataratas, anomalías refractivas, queratocono, retinopatía del prematuro, angiogénesis en la parte frontal del ojo, angiogénesis corneal después de queratitis, trasplante de córnea o queratoplastia, angiogénesis corneal debida a hipoxia (uso extenso de lentes de contacto), pterigión conjuntival, edema subretiniano y edema intrarretiniano.

10 16. La composición farmacéutica de la reivindicación 15 para el uso en el tratamiento o prevención de un trastorno oftalmológico seleccionado del grupo que comprende AMD seca, AMD húmeda o neovascularización coroidea (CNV).

15 17. Procedimiento para tratar o prevenir un trastorno oftalmológico seleccionado del grupo que comprende degeneración macular relacionada con la edad (AMD), neovascularización coroidea (CNV), membrana neovascular coroidea (CNMV), edema macular quístico (CME), membrana epirretiniana (MTC) y agujero macular, neovascularización coroidea asociada con miopía, estrías vasculares, desprendimiento de retina, retinopatía diabética, edema macular diabético (DME), cambios atróficos del epitelio pigmentario de la retina (RPE), cambios hipertróficos del epitelio pigmentario de la retina (RPE), oclusión venosa de la retina, oclusión de vena coroidea de la retina, edema macular, edema macular por oclusión venosa de la retina, retinitis pigmentaria, enfermedad de Stargardt, glaucoma, afecciones inflamatorias, cataratas, anomalías refractivas, queratocono, retinopatía del prematuro, angiogénesis en la parte frontal del ojo, angiogénesis corneal después de queratitis, trasplante de córnea o queratoplastia, angiogénesis corneal debida a hipoxia (uso extenso de lentes de contacto), pterigión conjuntival, edema subretiniano y edema intrarretiniano, que comprende administrar una composición farmacéutica de

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acuerdo con cualquiera de las reivindicaciones 1 a 13 que contiene una cantidad farmacéuticamente efectiva del agente activo.

18. Una composición farmacéutica oftalmológica tópica para el uso en el tratamiento o prevención de una enfermedad ocular posterior, en la que la
5 composición es una suspensión que comprende un agente activo aplicable para el tratamiento o prevención de una enfermedad ocular posterior suspendida en un vehículo farmacéuticamente aceptable aplicable.

19. La composición farmacéutica oftalmológica tópica de la reivindicación 18, en la que el vehículo farmacéuticamente aceptable es un vehículo no
10 acuoso.

20. La composición farmacéutica oftalmológica tópica de la reivindicación 18, en la que el vehículo farmacéuticamente aceptable es un vehículo hidrófobo.

21. La composición farmacéutica oftalmológica tópica de la reivindicación
15 20, en la que el vehículo farmacéuticamente aceptable se selecciona del grupo que comprende parafina líquida, parafina líquida ligera o una mezcla de las mismas.

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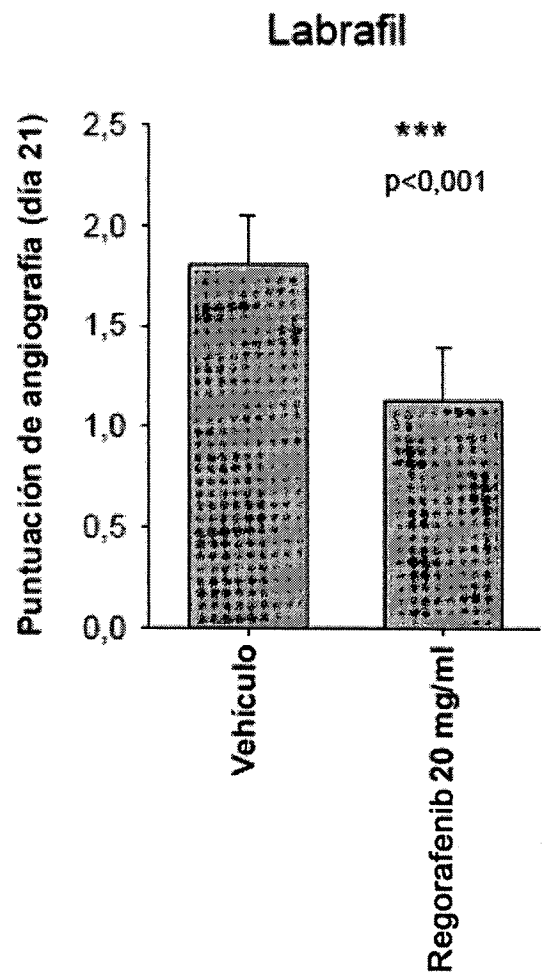
Composición oftalmológica tópica que contiene regorafenib

Resumen

La presente invención se refiere a composiciones farmacéuticas oftalmológicas tópicas que contienen regorafenib, un hidrato, solvato o sal
5 farmacéuticamente aceptable del mismo o un polimorfo del mismo y su procedimiento de preparación y su uso para el tratamiento de trastornos oftalmológicos.

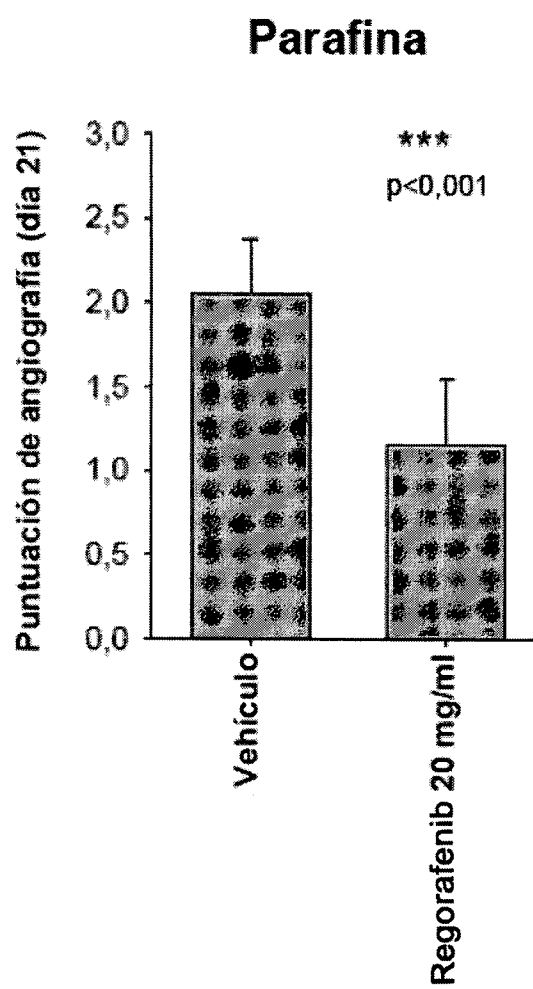
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Figura 1



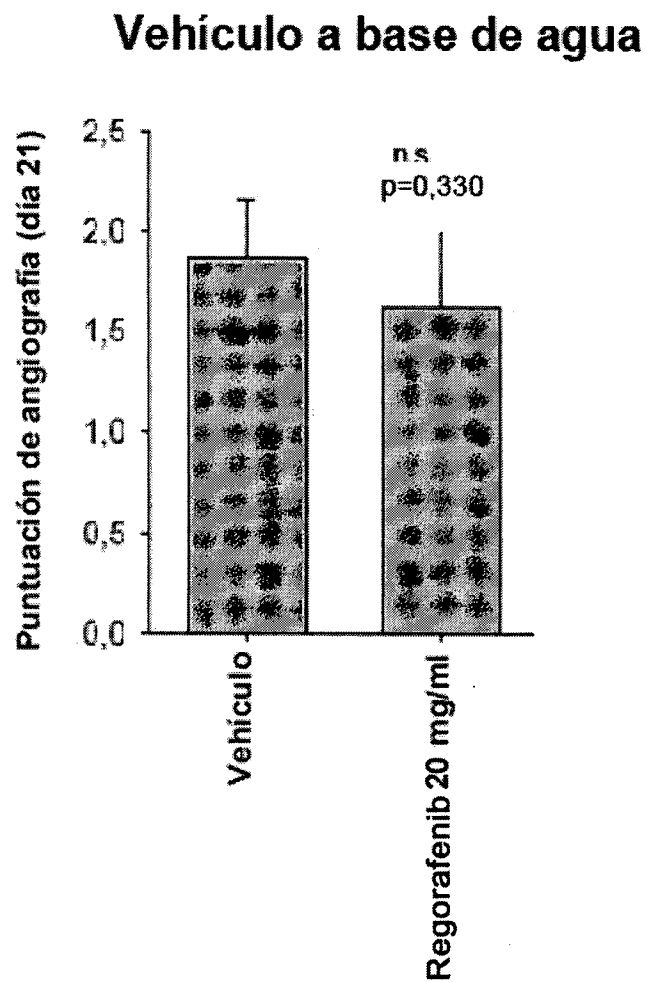
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Figura 2



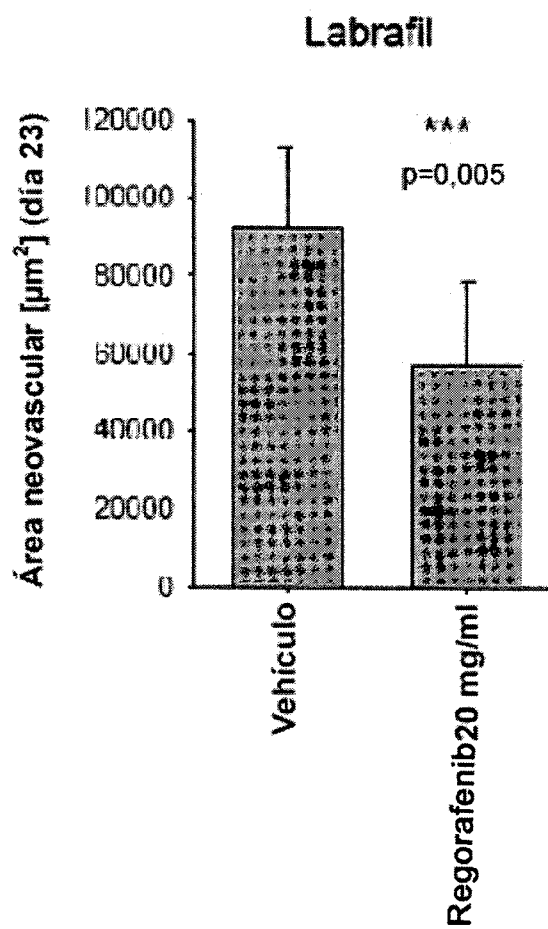
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Figura 3



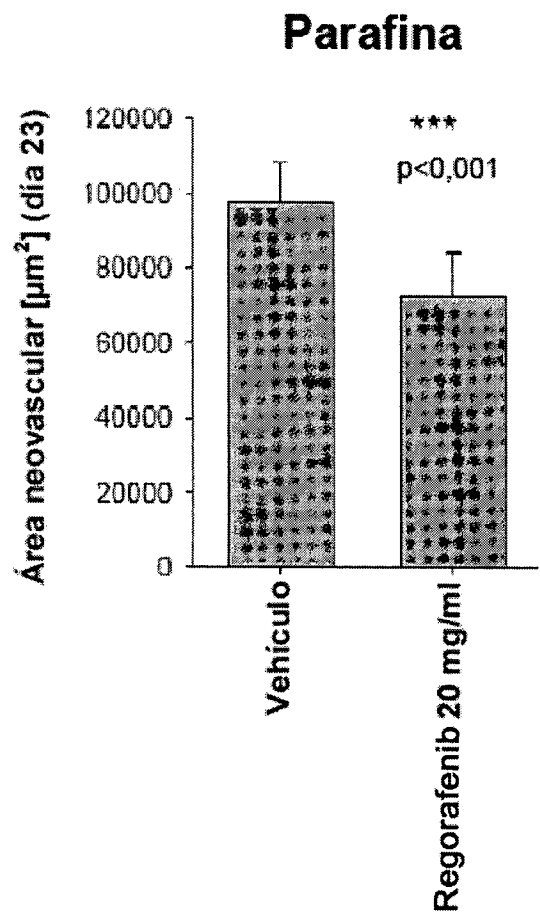
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Figura 4



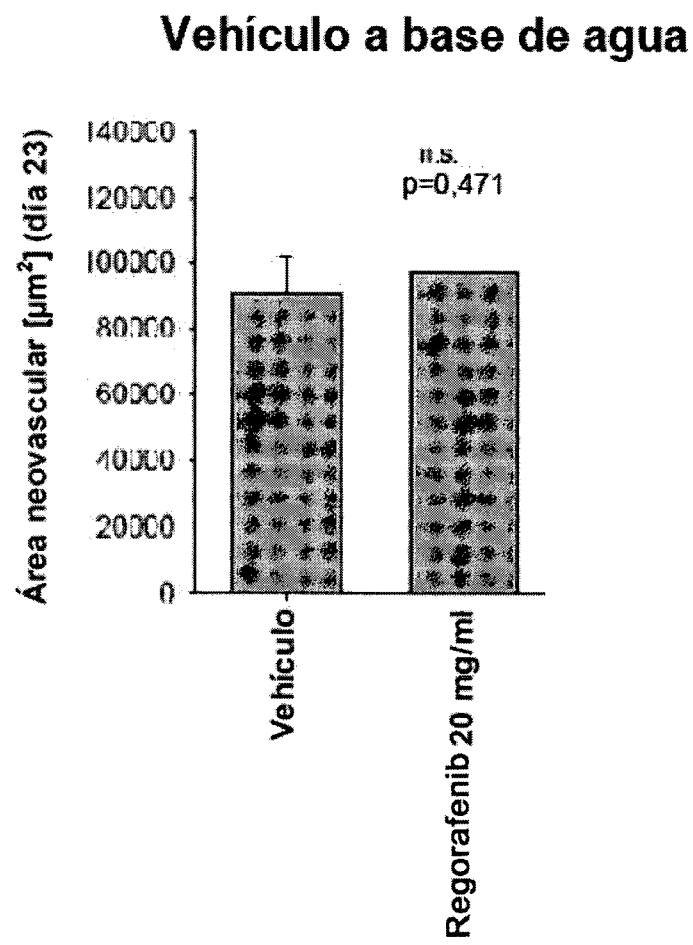
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Figura 5



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Figura 6



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(54) Title: TOPICAL OPHTHALMOLOGICAL PHARMACEUTICAL COMPOSITION CONTAINING REGORAFENIB

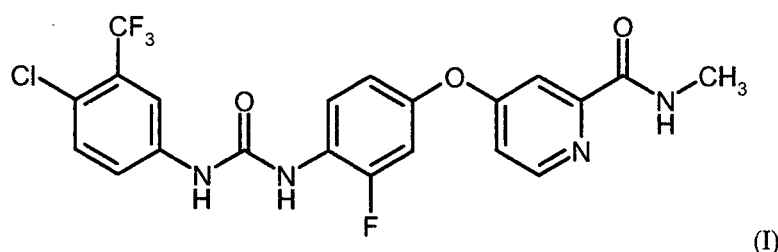
(57) Abstract: The present invention relates to topical ophthalmological pharmaceutical compositions containing regorafenib, a hydrate, solvate or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating ophthalmological disorders.

WO 2013/000917 A1

Topical Ophthalmological Pharmaceutical Composition containing Regorafenib

The present invention relates to topical ophthalmological pharmaceutical compositions containing regorafenib, a hydrate, solvate or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating ophthalmological disorders.

- 5 Regorafenib which is 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide, a compound of formula (I)



- is a potent anti-cancer and anti-angiogenic agent that possesses various activities including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signalling molecules and it can be used in treating various diseases and conditions like hyper-proliferative disorders such as cancers, tumors, lymphomas, sarcomas and leukemias as described in WO 2005/009961. Furthermore salts of the compound of formula (I) such as its hydrochloride, mesylate and phenylsulfonate are mentioned in WO 05/009961. The monohydrate of the compound of formula (I) is mentioned in WO 08/043446.

- 15 Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly population and is recognized as dry and wet AMD (Expert Opin. Ther. Patents (2010), 20(1), 103 – 11). The dry, or nonexudative, form involves both atrophic and hypertrophic changes of the retinal pigment epithelium (RPE). The dry form is characterized by macular drusen which are pigmented areas containing dead cells and metabolic products that distort the retina and eventually cause loss of acute vision. Patients with nonexudative AMD (dry form) can progress to the wet, or exudative or neovascular, AMD, in which pathologic choroidal neovascular membranes (CNVM) develop under the retina, leak fluid and blood, and, ultimately, cause a centrally blinding disciform scar over a relatively short time frame if left untreated. Choroidal neovascularization (CNV), the growth of new blood vessels from the choroid capillary network across the Bruch's membrane/RPE interface into the neural retina, results in retinal detachment, subretinal and intraretinal edema, and scarring.

Access to the choroid which is between the sclera and the retina other than via the blood is difficult. The eye is composed of three major anatomic compartments, the anterior chamber, posterior chamber, and vitreous cavity, that have limited physiological interaction with each other.

The retina is located in the back of the vitreous cavity, and is protected from the outside by the sclera which is the white, tough, impermeable wall of the eye. Choroidal blood flow is the usual method of carrying substances to the choroid and requires e.g. oral or intravenous administration of the drug. Most drugs cannot be delivered to the choroid by eye drops or a depot in vicinity to the eye. Some drugs have been delivered to the retina and thus to the choroid by injection into the vitreous chamber of the eye. The treatment of posterior eye diseases (back of the eye) by easily applicable topical eye formulations like eye drops is still an unsolved problem.

VEGF (vascular endothelial growth factor) is a key cytokine in the development of normal blood vessels as well as the development of vessels in tumors and other tissues undergoing abnormal angiogenesis and appears to play a central role in the pathogenesis of CNV formation (Expert Opin. Ther. Patents (2010), 20(1), 103-118, Expert Opin. Ther. Patents (2009), 18(10), 1573-1580, J. Clin. Invest. (2010), 120(9), 3033-3041, J. Cell. Physiol. (2008), 216, 29-37, New Engl. J. Med. 2006, 355, 1474-1485, WO 2010/127029, WO 2007/064752). Drugs which block the effects of VEGF are described for treating wet AMD such as aptamers like pegaptanib (New Engl. J. Med. 2004, 351, 2805-2816), or VEGF antibodies like ranibizumab (New Engl. J. Med. 2006, 355, 1419-1431) or bevacizumab (Ophthalmology, 2006, 113, 363-372). However, said drugs have to be administered intravitreally by injection into the eye. Sorafenib, a VEGF inhibitor as well, is described for treating CNV by oral administration (Clinical and Experimental Ophthalmology, 2010, 38, 718-726). Pazopanib, a VEGF inhibitor as well, is described for treating AMD by topical administration of eye drops containing an aqueous solution of Pazopanib (WO 2011/009016). WO 2006/133411 describes compounds for the treatment of CNV by topical administration of liposomal formulations. WO 2007/076358, US2006257487 describe aqueous ophthalmological formulations for topical administration. WO 2008/27341 describes emulsions for topical administration to the eye.

It is general expert knowledge that usually topical eye drops do not deliver therapeutic levels of drug molecules to the target tissues present at the back of the eye in order to treat posterior eye diseases (U.B. Kompella and H.F. Edelhauser, "Drug Product Development for the Back of the Eye", aapspress Springer, 2011, page 449).

Despite the progress described in the art there remains a need for improved medicines for the treatment of ophthalmological disorders like AMD. In particular, there remains a need for topical ophthalmological pharmaceutical compositions like eye drops which can be administered easily and therefore would increase the patient's compliance. Furthermore there is still the need of applicable topical ophthalmological pharmaceutical compositions for compounds having for example a low solubility which cannot be formulated in a simple solution, emulsion, as a complex or in a liposomal formulation. The topical ophthalmological pharmaceutical composition has to

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provide a concentration of the active agent in the eye which is sufficient for an effective therapy. This is dependent on the solubility and the release behavior of the active agent. In the case of a liquid formulation the dissolution properties and chemical stability of the active agent are of importance. In order to support a high compliance the topical ophthalmological pharmaceutical composition should not have to be taken in more than 5 times a day, the less the better. Type and amount of the excipients in combination with the process of preparation of the pharmaceutical composition are essential for release properties, bioavailability of the active agent in the eye, in particular in the back of the eye (e.g. in the area of the retina, Bruch's membrane and choroid), stability, compatibility, efficacy and the industrial applicability of the manufacturing process for the topical ophthalmological pharmaceutical composition.

The problem to be solved by the present invention is to provide a topical ophthalmological pharmaceutical composition comprising regorafenib as active agent which has a sufficient stability and compatibility and which achieves an effective concentration of regorafenib in the eye, in particular in the back of the eye for the treatment of ophthalmological disorders with sufficient efficacy by avoiding an intravenous or oral administration or injection into or close to the eye (e.g. intravitreal or other injections).

Another problem to be solved by the present invention is to provide a topical ophthalmological pharmaceutical composition for the treatment of a posterior eye disease.

Regorafenib monohydrate has a limited solubility profile. The thermodynamic solubility of regorafenib monohydrate in different solvents is shown in table 1:

Table 1:

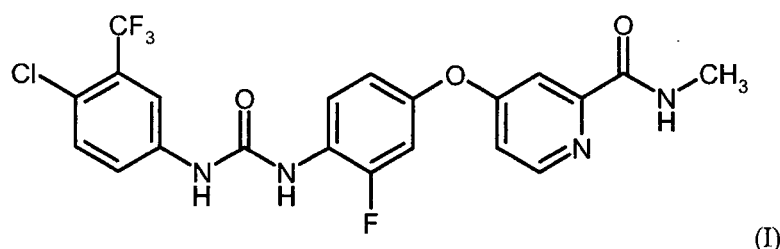
Solvent	Solubility (mg/ml)
Water	< 0.1
Ligth liquid paraffin	< 0.1
Ethanol	6.4
Polyethylenglycol (PEG) 400	67.3
HPB-Cyclodextrin/water (10:90)	< 0.1
PEG 400/water (30:70)	0.27
Oleoylpolyethylenglycol glycerides	3.6

Surprisingly the pharmaceutical composition according to the invention provides by topical administration a sufficient amount of the active agent into the eye which is effective for treating ophthalmological disorders. In particular, the pharmaceutical composition according to the invention provides the active agent in a sufficient amount into the back of the eye, i.e. that the pharmaceutical composition according to the invention effects the transportation of the active agent from the front of

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the eye to the back of the eye. Furthermore the pharmaceutical composition according to the invention has a sufficient stability without any meaningful degradation of the active agent and is compatible with the eye.

The present invention pertains to a topical ophthalmological pharmaceutical composition comprising regorafenib, the compound of the formula (I),



a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof and at least one pharmaceutically acceptable vehicle and optionally at least one pharmaceutically acceptable excipient.

Preference is given to a topical ophthalmological pharmaceutical composition comprising regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib or a polymorph thereof as active agent and at least one pharmaceutically acceptable vehicle and optionally at least one pharmaceutically acceptable excipient wherein the composition is a suspension comprising the active agent suspended in the applicable pharmaceutically acceptable vehicle.

A pharmaceutically acceptable vehicle or excipient is any vehicle or excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active agent so that any side effects ascribable to the vehicle or excipient do not vitiate the beneficial effects of the active agent.

The term "the compound of formula (I)" or "regorafenib" refer to 4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl}amino-3-fluorophenoxy}-N-methylpyridine-2-carboxamide as depicted in formula (I).

The term "compound of the invention" or "active agent" refer to regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof.

Solvates for the purposes of the invention are those forms of the compounds or their salts where solvent molecules form a stoichiometric complex in the solid state and include, but are not limited to for example ethanol and methanol.

Hydrates are a specific form of solvates, where the solvent molecule is water. Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds or salts with water, such as, for example, hemi-, mono- or dihydrates. Preference is given to the monohydrate of regorafenib.

- 5 Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid (tosylate salt), 1-
10 naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of
15 organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Preference is given to the hydrochloride, mesylate or
20 phenylsulfonate salt of regorafenib.

Preferred are regorafenib and the monohydrate of regorafenib, most preferred is regorafenib monohydrate as compounds of the present invention.

- Due to the low solubility of regorafenib, in particular of regorafenib monohydrate (see table 1) standard solutions are not applicable. Also solutions containing tolerable amounts of emulsifiers, solubilising
25 agents, complex forming excipients etc. are not available to provide for example sufficient stability of regorafenib.

The topical ophthalmological pharmaceutical composition according to the invention comprises the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in a solid form, preferably in a crystalline form, more preferably in a microcrystalline form.

- 30 Micronization can be achieved by standard milling methods, preferably by air jet milling, known to a skilled person. The microcrystalline form can have a mean particle size of from 0.5 to 10 μm , preferably from 1 to 6 μm , more preferably from 1 to 3 μm . The indicated particle size is the mean

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of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

The minimum concentration of the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in the topical ophthalmological pharmaceutical composition is 0.01 %, preferably 0.2 % by weight of the total amount of the composition. The maximum concentration of the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in the topical ophthalmological pharmaceutical composition is 10 %, preferably 5 %, more preferably 4 % by weight of the total amount of the composition.

Preference is given to a concentration of the compound of the present invention in the pharmaceutical composition from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

Particular preference is given to a concentration of regorafenib in the pharmaceutical composition from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

Particular preference is given to a pharmaceutical composition resulting from addition of regorafenib monohydrate in amounts from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

The topical ophthalmological pharmaceutical composition according to the invention includes but is not limited to eye drops, gels, ointments, dispersions or suspensions.

Preference is given to a topical ophthalmological pharmaceutical composition which is a suspension.

The compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate is used preferably in a micronized form.

Micronization can be achieved by standard milling methods, preferably by air jet milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 μm , preferably from 1 to 6 μm , more preferably from 2 to 3 μm . The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

One embodiment of the present invention is a topical ophthalmological pharmaceutical composition which is a suspension comprising the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in a solid form, preferably in a crystalline form, more preferably in a microfine crystalline form suspended in an applicable pharmaceutically acceptable vehicle, and optionally further comprising one or more pharmaceutically acceptable excipients.

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Preference is given to a suspension based on a non-aqueous vehicle, more preferably to a suspension based on a hydrophobic vehicle.

Suitable pharmaceutically acceptable vehicles according to the present invention include but are not limited to oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, hydrocarbon vehicles like liquid paraffin (Paraffinum liquidum, mineral oil), light liquid paraffin (low viscosity paraffin, Paraffinum perliquidum, light mineral oil), soft paraffin (vaseline), hard paraffin, vegetable fatty oils like castor oil, peanut oil or sesame oil, synthetic fatty oils like middle chain triglycerides (MCT, triglycerides with saturated fatty acids, preferably octanoic and decanoic acid), isopropyl myristate, caprylocaproyl macrogol-8 glyceride, caprylocaproyl polyoxyl-8 glycerides, wool alcohols like cetylstearylalcohols, wool fat, glycerol, propylene glycol, propylene glycol diesters of caprylic/capric acid, polyethyleneglycols (PEG), water like an aqueous isotonic sodium chloride solution or a mixture of thereof.

Preference is given to non-aqueous pharmaceutically acceptable vehicles which include but are not limited to middle chain triglycerides (MCT, triglycerides with saturated fatty acids, preferably octanoic and decanoic acid, isopropyl myristate, caprylocaproyl macrogol-8 glyceride, caprylocaproyl polyoxyl-8 glycerides, oleoyl polyethyleneglycol glycerides, oleoyl macrogol-6 glycerides (Labrafil M 1944 CS), linoleoyl macrogol-6 glycerides (Labrafil M2125 CS = linoleoyl polyoxyl-6 glycerides), lauroyl macrogol-6 glycerides (Labrafil M 2130 CS = lauroyl polyoxyl-6 glycerides)), hydrocarbon vehicles, fatty oils like castor oil or a mixture of thereof. Most preferably hydrophobic vehicles are used like hydrocarbon vehicles which include but are not limited to liquid paraffin or light liquid paraffin or a mixture thereof.

Very surprisingly the pharmaceutical composition according to the present invention comprising a lipophilic vehicle like liquid or light liquid paraffin provides by topical administration a sufficient amount of the active agent into the eye which is effective for treating ophthalmological disorders, although the solubility of regorafenib monohydrate in lipophilic vehicles is very low.

The pharmaceutically acceptable vehicle is the basis of the topical ophthalmological pharmaceutical composition according to the present invention and is present in the composition in a minimum concentration of 75%, preferably 80%, more preferably 85% and in a maximum concentration of 99.9%, preferably 99%, more preferably 98% by weight of the total amount of the composition.

The pharmaceutical composition according to the present invention may have different viscosities, so that in principle a range from low-viscosity system to pastes is conceivable. Preference is given to fluid systems which include low-viscosity and also higher-viscosity systems as long as they still flow under their own weight.

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Suitable further pharmaceutically acceptable excipients used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to stabilizers, surfactants, polymer based carriers like gelling agents, organic co-solvents, pH active components, osmotic active components and preservatives.

- 5 Suitable stabilizers used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to colloidal silica, hydrophilic and hydrophobic silicas.

Preference is given to hydrophobic silicas which are silicas which are not wetted by water; this means that they float on the water surface. Likewise suitable are hydrophobicized mixed oxides of silicon dioxide and aluminum oxide, but hydrophobic pure silicas are preferred. They are produced by mixing hydrophilic silica with silanes (halosilanes, alkoxysilanes, silazanes, siloxanes). This entails silanol groups being alkylated by alkyl groups preferably having one up to 18 carbon atoms, particularly preferably having one up to 8 carbon atoms, very particularly preferably having one up to 4 carbon atoms, especially by methyl groups. Examples of silanes used in the production of hydrophobic silicas are hexamethyldisilazane or, preferably, dimethyldichlorosilane. The appropriate hydrophobic silicas may be derived from precipitated, colloidal, precompact or pyrogenic silicas, with preference for pyrogenic silicas. For example, reaction of a hydrophilic silica with dimethyldichlorosilane results in hydrophobic Aerosil having the proprietary name Aerosil® R 972; this has a degree of methylation of 66% to 75% (determined by titration of the remaining silanol groups).

- 20 The hydrophobic silica is employed in the formulations typically in a proportion of 0.1 to 10% by weight, preferably employed with 0.5 to 5%, for example with 2 %, by weight of the total composition. Further suitable stabilizing and/ or gelling agents used in the topical ophthalmic pharmaceutical composition according to the present invention include but are not limited to propylene glycol monopalmitostearate, glyceryl monostearate, glyceryl dibehenate, glyceryl distearate, hard fat, polyvinylpyrrolidon, polyethylene, glycerol, polyoxyethylene stearates, sorbitan fatty acid esters, cholesterol, macrogol-20-glycerolmonostearat, poloxamer 124, isopropyl myristate, isopropyl palmitate, colloidal silica, hydrophobic colloidal silica, magnesium stearate, zinc stearate, aluminium stearate, lanolin alcohols, organoclays, petrolatum, polyoxyl 6 stearate.

- 30 Suitable surfactants used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to lipids such as phospholipids, phosphatidylcholines, lecithin, cardiolipins, fatty acids, phosphatidylethanolamines, phosphatides, tyloxapol, polyethylenglycols and derivatives like PEG 400, PEG 1500, PEG 2000, poloxamer 407, poloxamer 188, polysorbate 80, polysorbate 20, sorbitan laurate, sorbitan stearate, sorbitan palmitate or a mixture thereof, preferably polysorbate 80.

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Suitable polymer base carriers like gelling agents used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to cellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethyl cellulose (CMC), methylcellulose (MC), hydroxyethylcellulose (HEC), amylase and derivatives, amylopectins and derivatives, dextran and derivatives, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and acrylic polymers such as derivatives of polyacrylic or polymethacrylic acid like HEMA, carbopol and derivatives of the before mentioned or a mixture thereof.

Suitable organic co-solvents used in the pharmaceutical composition according to the invention include but are not limited to ethylene glycol, propylene glycol, N-methyl pyrrolidone, 2-pyrrolidone, 3-pyrrolidinol, 1,4-butanediol, dimethylglycol monomethylether, diethyleneglycol monomethylether, solketal, glycerol, polyethylene glycol, polypropylene glycol.

Suitable pH active components such as buffering agents or pH-adjusting agents used in the pharmaceutical composition according to the invention include but are not limited to disodium phosphate, monosodium phosphate, boric acid, sodium borate, sodium citrate, hydrochloric acid, sodium hydroxide.

The pH active components are chosen based on the target pH for the composition which generally ranges from pH 4 - 9.

Suitable osmotic active components used in the pharmaceutical composition according to the invention include but are not limited to sodium chloride, mannitol, glycerol.

Preservatives used in the pharmaceutical composition according to the invention include but are not limited to benzalkonium chloride, alkyldimethylbenzylammonium chloride, cetrimide, cetylpyridinium chloride, benzododecinium bromide, benzethonium chloride, thiomersal, chlorobutanol, benzyl alcohol, phenoxethanol, phenylethyl alcohol, sorbic acid, methyl and propyl parabens, chlorhexidine digluconate, EDTA or mixtures thereof.

Gelling agents, pH active agents and osmotic active agents are preferably used in the case of an aqueous pharmaceutically acceptable vehicle.

The amount of the suitable further pharmaceutically acceptable excipient in the suspension according to the present invention can be from 0.1 to 15 %, preferably from 0.5 to 10 %, more preferably from 1 to 5 % by the total weight of the suspension.

Preferably the amount of hydroxypropylmethylcellulose in the suspension according to the present invention can be from 0.05 to 15 %, preferably from 0.1 to 10 %, more preferably from 1 to 5 % by the total weight of the suspension.

Preferably the amount of polysorbate 80 in the suspension according to the present invention can be from 0.05 to 10 %, preferably from 0.1 to 7 %, more preferably from 0.5 to 4 % by the total weight of the suspension.

Preference is given to a topical ophthalmological pharmaceutical composition comprising crystalline regorafenib monohydrate, more preferably microcrystalline regorafenib monohydrate in a concentration of for example 0.01 to 10 %, more preferably 0.2 to 5 % weight of the total amount of the composition suspended in a pharmaceutically acceptable vehicle selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof optionally containing hydrophobic silica as stabilizer in an amount of 0.1 % to 10 %, preferably 0.5 to 5 %, for example with 2 %, by weight of the total composition.

Preference is also given to a topical ophthalmological pharmaceutical composition comprising crystalline regorafenib monohydrate, more preferably microfine crystalline regorafenib monohydrate in a concentration of for example 0.1 to 10 %, more preferably 0.2 to 5 % weight of the total amount of the composition suspended in oleoyl polyethyleneglycol glyceride as pharmaceutically acceptable vehicle optionally containing hydrophobic silica as stabilizer in an amount of 0.1 % to 10 %, preferably 0.5 to 5 %, for example with 2 %, by weight of the total composition.

The total amount of the active agent to be administered via the topical route into the eye using the pharmaceutical composition of the present invention will generally range from about 0.01 to 50 mg, preferably 0.02 to 10 mg, more preferably 0.05 to 5 mg per administration and per eye. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of ophthalmological disorders, by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art.

The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

The pharmaceutical composition according to the invention is administered one or more, preferably up to 5, more preferably up to 3 times per day.

The typical method of administration of the pharmaceutical composition according to the invention is the topical delivery into the eye.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on individual response to the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by preferably topical administration into the eye to a patient in need thereof, and will have advantageous properties in terms of drug release, bioavailability, and/or compliance in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

The pharmaceutical composition according to the invention is chemically stable for more than 18 months, preferably more than 24 months. Chemically stable according the present invention means that the active agent does not degrade significantly ($< 1\%$) during storage.

In this connection the topical ophthalmological pharmaceutical composition according to the invention contains 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.05%, that means from 0.001% to a maximum of 0.05%, preferably in an amount of equal or less than 0.025%, that means from 0.001% to a maximum of 0.025%, most preferably in an amount of equal or less than 0.01%, that means from 0.001% to a maximum of 0.01% by weight based on the amount of the compound of the formula (I).

Process for manufacturing

Various methods can be used to prepare the ophthalmological pharmaceutical composition according to the invention. First the pharmaceutically acceptable vehicle is prepared by optionally mixing the applicable vehicle or mixture of vehicles with the pharmaceutically acceptable excipients. Thereafter the active agent is dispersed or suspended into said mixture. The process may also include sterilization e.g. by sterile precipitation, gamma irradiation, sterile filtration, heat sterilization, aseptic filling, or a combination of such optional steps.

The present invention also relates to a process for the manufacturing of a topical ophthalmological pharmaceutical composition according to the invention, wherein the compound of the present

invention is suspended in an applicable pharmaceutically acceptable vehicle optionally in the presence of further one or more pharmaceutically acceptable excipients and the suspension is homogenized.

Preference is given to a process for the manufacturing of a topical ophthalmological pharmaceutical composition according to the invention, wherein

- 5 a) the applicable pharmaceutically acceptable vehicle or a mixture of applicable pharmaceutically acceptable vehicles is prepared by mixing the vehicles optionally in the presence of a further one or more pharmaceutically acceptable excipients,
- b) the compound of the present invention, preferably regorafenib, more preferably regorafenib monohydrate, is suspended into said applicable pharmaceutically acceptable vehicle or
10 mixture for example at room temperature, optionally in the presence of a further one or more pharmaceutically acceptable excipients,
- c) the suspension is homogenized by stirring, shaking or vortexing, preferably stirring, at room temperature,
- d) the suspension is subdivided into single units and filled into applicable vials, container,
15 tube, flask, dropper and/or syringe.

Optionally in step a) the further one or more pharmaceutically acceptable excipients are added to the applicable pharmaceutically acceptable vehicle at elevated temperatures for example of 40 to 70°C.

Method of treating ophthalmological disorders

20 The present invention also relates to a use of the pharmaceutical composition according to the invention to treat or prevent ophthalmological disorders.

Furthermore the present invention also relates to a method for treating or preventing an ophthalmological disorder comprising administering a pharmaceutical composition containing a pharmaceutically effective amount of an active agent according to the present invention.

Examples of ophthalmological disorders according to the invention include but are not limited to
25 age-related macular degeneration (AMD), choroidal neovascularization (CNV), choroidal neovascular membrane (CNVM), cystoid macula edema (CME), epi-retinal membrane (ERM) and macular hole, myopia-associated choroidal neovascularisation, vascular streaks, retinal detachment, diabetic retinopathy, diabetic macular edema (DME), atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), retinal vein
30 occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, retinitis pigmentosa, Stargardt's disease, glaucoma, inflammatory conditions of the eye

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such as e.g. uveitis, scleritis or endophthalmitis, cataract, refractory anomalies such as e.g. myopia, hyperopia or astigmatism and ceratoconus and retinopathy of prematurity. In addition, examples include but are not limited to angiogenesis in the front of the eye like corneal angiogenesis following e.g. keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to
5 hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema. Examples of age-related macular degeneration (AMD) include but are not limited to dry or nonexudative AMD, or wet or exudative or neovascular AMD.

Preference is given to age-related macular degeneration (AMD) like dry AMD, wet AMD or choroidal neovascularization (CNV).

10 Another embodiment of the present invention is a topical ophthalmological pharmaceutical composition for the treatment or prevention of a posterior eye disease wherein the composition is a suspension comprising an active agent applicable for the treatment or prevention of a posterior eye disease suspended in a applicable pharmaceutically acceptable vehicle.

Preference is given to a suspension based on a non-aqueous vehicle, more preferably to a suspension
15 based on a hydrophobic vehicle.

Examples of posterior eye diseases include but are not limited to age-related macular degeneration (AMD), choroidal neovascularization (CNV), choroidal neovascular membrane (CNVM), cystoid macula edema (CME), epi-retinal membrane (ERM) and macular hole, myopia-associated choroidal neovascularisation, vascular streaks, retinal detachment, diabetic retinopathy, diabetic
20 macular edema (DME), atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), retinal vein occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, retinitis pigmentosa, Stargardt's disease and retinopathy of prematurity.

Preferred posterior eye diseases include age-related macular degeneration (AMD) like dry AMD,
25 wet AMD or choroidal neovascularization (CNV).

Examples of age-related macular degeneration (AMD) include but are not limited to dry or nonexudative AMD, or wet or exudative or neovascular AMD.

Active agents applicable for the treatment or prevention of a posterior eye disease according to the present invention include but are not limited to signal transduction inhibitors targeting receptor kinases
30 of the domain families of e.g. VEGFR, PDGFR, FGFR and their respective ligands or other pathway inhibitors like VEGF-Trap (aflibercept), pegaptanib, ranibizumab, pazopanib, bevasiranib, KH-902, mecamlamine, PF-04523655, E-10030, ACU-4429, volociximab, sirolimus, fenretinide, disulfiram,

sonenpcizumab, regorafenib, sorafenib and/or tandospirone. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189),
5 SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American
10 Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539), PKC412, nepafenac.

Preference is given to regorafenib, bevacizumab, aflibercept, pegaptanib, ranibizumab, pazopanib
15 and/or bevasiranib.

Suitable pharmaceutically acceptable vehicles according to the present invention include but are not limited to oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, hydrocarbon vehicles like liquid paraffin (Paraffinum liquidum, mineral oil), light liquid paraffin (low viscosity paraffin, Paraffinum perliquidum, light mineral oil),
20 soft paraffin (vaseline), hard paraffin, vegetable fatty oils like castor oil, peanut oil or sesame oil, synthetic fatty oils like middle chain triglycerides (MCT, triglycerides with saturated fatty acids, preferably octanoic and decanoic acid), isopropyl myristate, caprylocaproyl macrogol-8 glyceride, caprylocaproyl polyoxyl-8 glycerides, wool alcohols like cetylstearylalcohols, wool fat, glycerol, propylene glycol, propylene glycol diesters of caprylic/capric acid, polyethyleneglycols (PEG) or a
25 mixture of thereof.

Preference is given to non-aqueous pharmaceutically acceptable vehicles which include but are not limited to middle chain triglycerides (MCT, triglycerides with saturated fatty acids, preferably octanoic and decanoic acid, isopropyl myristate, caprylocaproyl macrogol-8 glyceride, caprylocaproyl polyoxyl-8 glycerides, oleoyl polyethyleneglycol glycerides, oleoyl macrogol-6
30 glycerides (Labrafil M 1944 CS), linoleoyl macrogol-6 glycerides (Labrafil M2125 CS = linoleoyl polyoxyl-6 glycerides), lauroyl macrogol-6 glycerides (Labrafil M 2130 CS = lauroyl polyoxyl-6 glycerides)), hydrocarbon vehicles, fatty oils like castor oil or a mixture of thereof. Most preferably hydrophobic vehicles are used like hydrocarbon vehicles which include but are not limited to liquid paraffin or light liquid paraffin or a mixture thereof.

Very surprisingly the suspension according to the present invention comprising a lipophilic vehicle like liquid or light liquid paraffin provides by topical administration a sufficient amount of the active agent to the back of the eye which is effective for treating a posterior eye disease.

Suitable further pharmaceutically acceptable excipients used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to stabilizers, surfactants, polymer based carriers like gelling agents, organic co-solvents, pH active components, osmotic active components and preservatives.

Suitable stabilizers used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to colloidal silica, hydrophilic and hydrophobic silicas.

10 Preference is given to hydrophobic silicas.

The pharmaceutically acceptable vehicle is the basis of the topical ophthalmological pharmaceutical composition according to the present invention and is present in the composition in a minimum concentration of 75%, preferably 80%, more preferably 85% and in a maximum concentration of 99.9%, preferably 99%, more preferably 98% by weight of the total amount of the composition. The active ingredient used in the topical ophthalmological pharmaceutical composition is used preferably in a micronized form.

Micronization can be achieved by standard milling methods, preferably by air jet milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 μm , preferably from 1 to 6 μm , more preferably from 2 to 3 μm . The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

The concentration of the active ingredient in the pharmaceutical composition is from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

The pharmaceutical composition according to the invention can be administered as the sole pharmaceutical composition or in combination with one or more other pharmaceutical compositions or active agents where the combination causes no unacceptable adverse effects.

“Combination” means for the purposes of the invention not only a dosage form which contains all the active agents (so-called fixed combinations), and combination packs containing the active agents separate from one another, but also active agents which are administered simultaneously or sequentially, as long as they are employed for the prophylaxis or treatment of the same disease.

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Since the combination according to the invention is well tolerated and is potentially effective even in low dosages, a wide range of formulation variants is possible. Thus, one possibility is to formulate the individual active ingredients of the combination according to the invention separately. In this case, it is not absolutely necessary for the individual active ingredients to be taken at the same time; on the contrary, sequential intake may be advantageous to achieve optimal effects. It is appropriate with such separate administration to combine the formulations of the individual active ingredients simultaneously together in a suitable primary packaging. The active ingredients are present in the primary packaging in each case in separate containers which may be, for example, tubes, bottles or blister packs. Such separate packaging of the components in the joint primary packaging is also referred to as a kit.

In one embodiment, the pharmaceutical compositions of the present invention can be combined with other ophthalmological agents. Examples of such agents include but are not limited to carotenoids like lycopene, lutein, zeaxanthin, phytoene, phytofluene, carnosic acid and derivatives thereof like carnosol, 6,7-dehydrocarnosic acid, 7-ketocarnosic acid, a zinc source like zinc oxide or a zinc salt like its chloride, acetate, gluconate, carbonate, sulphate, borate, nitrate or silicate salt, copper oxide, vitamin A, vitamin C, vitamin E and/or β -carotene.

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors targeting receptor kinases of the domain families of e.g. VEGFR, PDGFR, FGFR and their respective ligands or other pathway inhibitors like VEGF-Trap (aflibercept), pegaptanib, ranibizumab, pazopanib, bevasiranib, KH-902, mecamlamine, PF-04523655, E-10030, ACU-4429, volociximab, sirolimus, fenretinide, disulfiram, sonopizumab and/or tandospirone. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539), PKC412, nepafenac.



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Preference is given to a combination with bevacizumab, aflibercept, pegaptanib, ranibizumab, pazopanib and/or bevasiranib.

Generally, the use of the other ophthalmological agents in combination with the pharmaceutical compositions of the present invention will serve to:

- 5 (1) yield better efficacy as compared to administration of either agent alone,
- (2) provide for the administration of lesser amounts of the administered agents,
- (3) provide for treating a broader spectrum of mammals, especially humans,
- (4) provide for a higher response rate among treated patients,
- (5) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to
- 10 known instances where other agent combinations produce antagonistic effects. It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

- 15 All publications, applications and patents cited above and below are incorporated herein by reference.

The weight data are, unless stated otherwise, percentages by weight and parts are parts by weight.

Examples:

HPLC Methods:

- Two separate HPLC methods were developed for the determination of regorafenib content, unidentified degradation products and unidentified secondary components, as well as for the
- 20 determination of the specific degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA), respectively, within pharmaceutical formulations.

- 1) HPLC method for the determination of regorafenib content, unidentified secondary components, and unidentified degradation products: Samples were prepared by dilution of drawn formulation
- 25 aliquots with water/acetonitrile (25/75) to a final regorafenib concentration of 100µg/ml. 10µl of each sample were injected into an Agilent 1100 HPLC system (Agilent, Waldbronn, Germany), and samples were run on a heated (40°C) Symmetry C18 column (150 x 4,6mm - 3,5µm particle size, Waters, Eschborn, Germany) applying a flow rate of 1ml/min. The mobile phase consisted of a

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mixture of potassium phosphate buffer pH 2.4 (A) and acetonitrile/ethanol (6/4) (B). The following gradient was applied: minute 0: A, 60% / B, 40%; minute 12: A, 20% / B, 80%; minute 16: A, 20% / B, 80%; minute 16.5: A, 60% / B, 40%; minute 20: A, 60% / B, 40%. Regorafenib, unidentified secondary components, and unidentified degradation products were quantified using a DAD
5 detector at a wavelength of 265 nm. Regorafenib content (column 3 in tables below) within formulations was quantified by using an external 2-point calibration straight line. Unidentified secondary components and unidentified degradation products (columns 5-7 in tables below) are described as % of summarized sample-related peak areas. Precision of the system was determined with each sample set run, by six times injection of a 100% regorafenib standard (e.g. 100µg/ml),
10 coefficient of variation of peak areas resulting from these six injections was always below 2%. Relative Y-axis intercept of a 2-point (e.g. 50µg/ml, 100µg/ml) calibration straight line was always below 3% (referring to 100% Regorafenib standard). The regorafenib peak appears at 11.5 minutes.

Alternatively (examples 3 - 5), the content of regorafenib and its degradation products is determined by a different but similar HPLC method, using 100 mm x 4.6 mm reversed phase
15 columns (YMC Pack Pro RS C18, 3 µm particle size). Samples of 5 µl with a nominal content of 0.16 mg/ml were injected and eluted with a mobile phase gradient consisting of trifluoro acetic acid (2 ml per liter of water) (A) and acetonitrile (B) at a flow rate of 1.0 ml/min. The following gradient conditions were applied: 0 - 1 min 75% A / 25 % B; until 3.5 min changed to 50 % A / 50 % B; until 11.5 min changed to 43 % A / 57 % B; until 13 min changed to 15 % A / 85 % B and
20 kept until 16 min at 15 % A / 85 % B, followed by re-equilibration to 75% A / 25 % B. The column temperature was 40°C and the detection wavelength was 260 nm (using diode array detection). The quantitation of regorafenib was done via external standard with 3-point calibration. The degradation products are quantified using the same calibration function obtained with regorafenib reference standard. This HPLC method is fully validated for a solid oral dosage for containing
25 regorafenib and meets all requirements with respect to selectivity, precision, linearity and robustness. The elution time for the regorafenib peak is about the same as for the method described above

2) HPLC method for the determination of the specific degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA). Samples were prepared by dilution of drawn
30 formulation aliquots with acetone to a final regorafenib concentration of 3000µg/ml. 15µl of each sample were injected into an Agilent 1100 HPLC system (Agilent, Waldbronn, Germany), and samples kept at 10° in the autosampler were run on a Symmetry C18 column (150 x 4,6mm - 3,5µm particle size, Waters, Eschborn, Germany) held at 20°C with a flow rate of 1ml/min. The
35 mobile phase consisted of a mixture of potassium phosphate buffer pH 2.4 (A) and

acetonitrile/ethanol (6/4) (B). The following gradient was applied: minute 0: A, 62% / B, 38%; minute 5: A, 44% / B, 56%; minute 5.01: A, 15% / B, 85%; minute 9: A, 15% / B, 85%; minute 9.01: A, 62% / B, 38%; minute 12: A, 62% / B, 38%. 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (column 4 in tables below) was quantified using a DAD detector at a wavelength of 232 nm, referring to an external 3-point (e.g. 0.04µg/ml, 0.1µg/ml, 1µg/ml) calibration straight line. The 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide peak appears at 3.9 minutes. Limit of detection (LOD) and limit of quantification (LOQ) of 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide were determined for two different matrices (water and paraffin), and were: LOD: 4ppm = 0.0004% (water), 13ppm = 0.0013% (paraffin); LOQ: 13ppm = 0.0013% (water) and 43ppm = 0.0043% (paraffin).

Example 1: Ophthalmological suspension comprising regorafenib monohydrate in oleoyl polyethyleneglycol glyceride (20 mg/ml)

200 mg of micronized regorafenib monohydrate was suspended in oleoyl polyethyleneglycol glyceride (10 ml). The suspension was homogenized by stirring at room temperature for 15 minutes.

Stability of regorafenib in oleoyl polyethyleneglycol glyceride was tested at a concentration of 3 mg/ml over 4 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 95.0-101% of theoretical concentration, largest unidentified degradation product ranged from 0.3 to 0.7%. 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA) content was below < 13 ppm = 0.0013% (< LOD determined for paraffin based formulation, Table 2). For analytical details see HPLC Method section above.

Table 2. Content and stability of regorafenib within oleoyl polyethyleneglycol glyceride based formulation:

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (% referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		95.0	< 0.0013	0.04	0.04	0.7

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1 day	25°C / 60% r.h.	101	< 0.0013	0.04	0.04	0.6
4 weeks	25°C / 60%r.h.	99.0	< 0.0013	0.04	0.04	0.3
4weeks	40°C / 75%r.h.	98.7	< 0.0013	0.04	0.04	0.3

Example 2: Ophthalmological suspension comprising regorafenib monohydrate in liquid paraffin (20 mg/ml)

5 400 mg of micronized regorafenib monohydrate was suspended in 20 ml of light liquid paraffin. The suspension was homogenized by stirring at room temperature for 15 minutes.

Stability of the suspension was tested at a concentration of 20mg/ml over 13 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 74.8-99.6% of theoretical concentration. The observed fluctuation is most likely due to inhomogeneity of the sample after manual shaking of the suspension. No unidentified degradation product was observed in chromatograms. AFP-PMA content was below < 43 ppm = 0.0043% (< LOQ determined for paraffin based formulation, Table 3). For analytical details see Analytics section above.

10

Table 3. Content and stability of regorafenib within paraffin based formulation.

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (% referring to Regorafenib) , via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		99.6	< 0.0043	0.04	0.04	-
4 weeks	25°C/60 %r.h.	85.4	< 0.0043	0.04	0.04	-
4 weeks	40°C/75	74.8	< 0.0043	0.04	0.04	-

	%r.h.					
13 weeks	25°C/60 %r.h.	96.9	< 0.0043	0.04	0.04	-
13 weeks	40°C/75 %r.h.	94.6	< 0.0043	0.04	0.04	-

Example 3: Ophthalmological suspension comprising regorafenib monohydrate and 0.5% hydrophobic colloidal silica in liquid paraffin (20 mg/ml)

- 5
- 0.25 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (50 ml) by stirring at room temperature to prepare the suspending vehicle (0.5% (w/v) hydrophobic colloidal silica in light liquid paraffin). 200 mg of regorafenib monohydrate was added to an aliquot of the suspending vehicle (10 ml) and the suspension was homogenized for 45 min. using a vibration mill at a frequency of 9.1 s⁻¹.
- 10
- Afterwards, the suspension was filled into glass vials (approximately 6 ml per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps.
- Stability of the suspension was tested over 4 weeks at 4°C, room temperature (approx. 25°C) and 40°C/ 75% relative humidity (see Table 4). The variation and apparent higher concentrations relating to the nominal content (between 100 and 125 %) is most likely due to an artefact in sample preparation for analytics. The mode of sample preparation of silica-containing suspensions has
- 15
- been optimized subsequently as described in example 4 b).

Table 4. Content and stability of Regorafenib within Example 3 formulation

Storage condition	Content Regorafenib ¹ (g/l)	Content Regorafenib (% of nominal)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
4°C	21.07	109.3	0.05	<0.005	0.05
RT	24.13	125.2	0.05	<0.005	0.05
40°C/ 75 % r.h.	19.41	100.7	<0.05	<0.005	<0.05

¹ based on anhydrous drug substance

20

Example 4: Ophthalmological suspension comprising regorafenib monohydrate and 2% hydrophobic colloidal silica in liquid paraffin (20 mg/ml)

a)

1 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (50 mL) by stirring at room temperature to prepare the suspending vehicle (2% (w/v) hydrophobic colloidal silica in light liquid paraffin). 200 mg of regorafenib monohydrate was added to an aliquot of the suspending vehicle (10 mL) and the suspension was homogenized for 45 min. using a vibration mill at a frequency of 9.1 s⁻¹.

Afterwards, the suspension was filled into glass vials (approximately 6 mL per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps.

Stability of the suspension was tested over 4 weeks at 4°C, room temperature (approx. 25°C) and 40°C/ 75% relative humidity (see Table 5). The variation and apparent higher concentrations relating to the nominal content (between 104 and 118 %) is most likely due to an artefact in sample preparation for analytics. The mode of sample preparation of silica-containing suspensions has been optimized subsequently as described in example 4 b).

Table 5. Content and stability of Regorafenib within Example 4 a) formulation

Storage condition	Content Regorafenib ¹ (g/l)	Content Regorafenib (% of nominal)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
4°C	20.01	103.8	<0.05	<0.005	<0.05
RT	21.84	113.3	0.05	<0.005	0.05
40°C/ 75 % r.h.	22.67	117.6	0.05	<0.005	0.05

¹ based on anhydrous drug substance

b)

10 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (500 mL) at room temperature for 15 minutes using a high shear mixer (10230 rpm) to prepare the suspending vehicle (2% (w/v) hydrophobic colloidal silica in light liquid paraffin). 9 g of regorafenib monohydrate was added to an aliquot of the suspending vehicle (450 mL) and the suspension was homogenized for 45 minutes using a high shear mixer (10230 rpm).

The suspension was filled into glass vials (5 mL per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps. Afterwards, the vials were irradiated by gamma-radiation at an effective dose of 27.9 kGy.

Stability of the radiated suspension was tested over 4 weeks at 40°C/ 75% relative humidity (see Table 6). The mode of sample preparation of silica-containing suspensions was optimized at this

time point. The content of Regorafenib ranged between 98 and 103 % of the nominal content. AFP-PMA content was below 0.005 % (50 ppm).

5

Table 6. Content and stability of Regorafenib within Example 4 b) formulation

Storage time	Gamma radiation (27.9 kGy)	Storage condition	Content Regorafenib ¹ (g/l)	Content Regorafenib (% of nominal)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
0	No	-	19.51	101.2	0.05	<0.005	0.05
0	Yes	-	18.96	98.3	0.05	<0.005	0.05
4	Yes	40°C/ 75 % r.h.	19.74	102.4	0.05	<0.005	0.1

¹ based on anhydrous drug substance

10 **Example 5:** Ophthalmological suspension comprising regorafenib monohydrate and 5% hydrophobic colloidal silica in liquid paraffin (20 mg/ml)

2.5 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (50 mL) by stirring at room temperature to prepare the suspending vehicle (5% (w/v) hydrophobic colloidal silica in light liquid paraffin). 200 mg of regorafenib monohydrate was added to an aliquot of the suspending vehicle (10 mL) and the suspension was homogenized for 45 min. using a vibration mill at a frequency of 9.1 s⁻¹.

Afterwards, the suspension was filled into glass vials (approximately 6 mL per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps.

Stability of the suspension was tested over 4 weeks at 4°C, room temperature (approx. 25°C) and 40°C/ 75% relative humidity (see Table 7). The variation in the content (between 99 and 97 %) is most likely due to an artefact in sample preparation for analytics. The mode of sample preparation of silica-containing suspensions has been optimized subsequently as described in example 4 b).

Table 7. Content and stability of Regorafenib within Example 5 formulation

Storage condition	Content Regorafenib ¹ (g/l)	Content Regorafenib (% of nominal)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
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4°C	19.14	99.3	<0.05	<0.005	<0.05
RT	18.55	96.2	<0.05	<0.005	<0.05
40°C/ 75 % r.h.	18.76	97.3	<0.05	<0.005	<0.05

¹ based on anhydrous drug substance

Example 6: Ophthalmological suspension comprising regorafenib monohydrate in water based vehicle (20 mg/ml)

5 1.7 g of hydroxypropymethylcellulose 15 cp (HPMC) was dispersed in isotonic sodium chloride solution (48 g, 0.9% NaCl in water) at 70°C. The mixture was cooled down to room temperature while stirring. At room temperature evaporated water, and subsequently polysorbate 80 (0.5 g) was added and dissolved under moderate stirring. 518 mg of regorafenib monohydrate was added to an aliquot of the prepared vehicle (24.5g) and the suspension was homogenized by gently stirring at
10 room temperature for 15 minutes.

Stability of the suspension was tested at a concentration of 10 mg/ml over 13 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 103-112% of theoretical concentration. The observed fluctuation is most likely due to inhomogeneity of the sample after manual shaking of the suspension. Largest unidentified degradation product was <
15 0.1% of summarized sample related peak areas. Amount of AFP-PMA was determined only after 9 weeks storage.

Table 8. Content and Stability of Regorafenib within water based formulation.

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (%) of theoretical), via external calibration	AFP-PMA content (%) referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		103	n.d.	0.04	0.04	-
4 weeks	25°C/60 %r.h.	104	n.d.	0.1	0.04	-
4weeks	40°C/75	112	n.d.	0.1	0.04	-

	%r.h.					
9 weeks	25°C/60 %r.h.		0.0056			
9 weeks	40°C/75 %r.h.		0.0086			
13 weeks	25°C/60 %r.h.	104	n.d.	0.06	0.04	-
13 weeks	40°C/75 %r.h.	104	n.d.	0.06	0.04	-

In tables 2, 3 and 8 above column 5 describes the percental amount of the largest unidentified secondary component in the standard used in the HPLC method to be compared with the value of column 6 which describes the percental amount of the same unidentified secondary component in the formulation. Column 7 describes the percental amount of the largest unidentified degradation product in the formulation which is not AFP-PMA. Said degradation product is not detectable in the standard but is formed in the formulation.

10 **Example 7:** **Ophthalmological suspension comprising regorafenib monohydrate in middle chain triglycerides (MCT, miglyol) (20 mg/ml)**

Example 7 was prepared according to example 1.

Table 9. Content and stability of regorafenib within MCT- based formulation.

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (% referring to Regorafenib) , via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)

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0		106.0	<0.0043	<0.1	<0.1	<0.1
4 weeks	25°C/60 %r.h.	99.5	<0.0043	<0.1	<0.1	<0.1
4 weeks	40°C/75 %r.h.	101.8	<0.0043	<0.1	<0.1	<0.1
13 weeks	25°C/60 %r.h.	101.0	<0.0043	<0.1	<0.1	<0.1
13 weeks	40°C/75 %r.h.	101.5	<0.0043	<0.1	<0.1	<0.1

Example 8: Ophthalmological suspension comprising regorafenib monohydrate in oculentum simplex (20 mg/g)

100 mg of micronized regorafenib monohydrate was suspended in 4900 mg oculentum simplex
5 (composition: cholesterole 1%, liquid paraffin 42.5%, soft paraffin 56.5% by weight). The suspension was homogenized by stirring at room temperature in an Agate motar for approximately 1 minute.

Example 9: Topical efficacy of different formulations containing regorafenib in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether twice daily topical administration (eye drops) of the topical ophthalmological pharmaceutical compositions according to the invention results in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation (Dobi et al, Arch. Ophthalmol. 1989, 107(2), 264-269 or Frank et al,
15 Curr. Eye Res. 1989 Mar, 8(3), 239-247)

For this purpose, a total of 133 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly assigned to eight groups of six to eight animals each. On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg / kg xylazine and 80 mg / kg ketamine (dissolved in water containing 5 mg/ml chlorobutanol hemihydrate and propylenglycol)
20 After instillation of one drop of 0.5 % atropin (dissolved in 0.9 % saline containing Benzalkoniumchloride) to dilate the pupils, choroidal neovascularisation was induced by burning six holes in the retina (disruption of Bruch's membrane) of one eye per animal (lesion size: 50 µm, laser intensity: 150 mW; stimulus duration: 100 ms) using a 532 nm argon laser.

The following formulations were included:

- a) 100 % oleoyl polyethyleneglycol glycerides as used in example 1 (vehicle control), n=8
- b) Example 1 (20 mg/ml, suspension), n=8
- 5 c) 100 % light liquid paraffin as used in example 2 (vehicle control), n=8
- d) Example 2 (20 mg/ml, suspension), n=8
- e) Water-based vehicle (Hydroxypropymethylcellulose 15 cp 3.5%, polysorbate 80 0.5%, isotonic NaCl solution 96% as used in example 6 (vehicle control), n=6
- f) Example 6 (20 mg/ml, suspension), n=6
- 10 g) 0.5 % hydrophobic colloidal silica in liquid paraffin as used in example 3 (vehicle control), n=10
- h) Example 3 (20 mg/ml, suspension), n=10
- i) 2.0% hydrophobic colloidal silica in liquid paraffin as used in example 4 (vehicle control), n=10
- 15 j) Example 4 (20 mg/ml, suspension), n=10
- k) 5.0% hydrophobic colloidal silica in liquid paraffin as used in example 5 (vehicle control), n=10
- l) Example 5 (20 mg/ml, suspension), n=10
- m) 100 % Miglyol as used in example 7 (vehicle control), n=8
- 20 n) Example 7 (20 mg/ml, suspension), n=7
- o) 100 % oculentum simplex as used in example 8 (vehicle control), n=8
- p) Example 8 (20 mg/g, suspension), n=6

Of each formulation, 10 µl were applied to the affected eye twice daily at an 10:14 hour interval during the complete observation period of 23 days. The body weight of all animals was recorded before the start and once daily during the study. An angiography was performed on day 21 using a fluorescence fundus camera (Kowe Genesis Df, Japan). Here, after anesthesia and pupillary

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dilation, 10 % sodium fluorescein (dye, dissolved in water) was subcutaneously injected and pictures were recorded approximately 2 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by three different examiners who were blinded for group allocation (examples 1 to 3 versus respective vehicle). Each lesion was scored with 0 (no leakage) to 3 (strongly stained), and a mean from all 6 lesions was used as the value for the respective animal. On day 23, animals were sacrificed and eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, and the sclera-choroid complex was washed, blocked and stained with a FITC-isolectine B4 antibody in order to visualize the vasculature. Then, the sclera-choroids were flat-mounted and examined under a fluorescence microscope (Keyence Biozero) at 488 nm excitation wavelength. The area (in μm^2) of choroidal neovascularization was measured using ImageTool software.

Results:

A) Efficacy regarding vascular leakage (angiography scores day 21):

Fig. 1: Angiography scores of vehicle (oleoyl polyethyleneglycol glycerides (Labrafil), formulation a) and regorafenib (example 1, formulation b) treated animals at day 21. Data are presented as mean $\pm$ SD, p-value according to t-test. N=8 per group.

Table 10: Raw data of the histogram depicted in Fig. 1. Single values represent the means from three different observers blinded with respect to treatment.

Animal	100% oleoyl polyethyleneglycol glycerides (formulation a)	Example 1 (formulation b)
1	1.80	1.14
2	1.72	0.67
3	1.63	1.44
4	1.72	0.90
5	1.67	1.00
6	2.00	1.22
7	1.56	1.33
8	2.33	1.33

Fig. 2: Angiography scores of vehicle (paraffin, formulation c) and regorafenib (example 2, formulation d) treated animals at day 21. Data are presented as mean $\pm$ SD, p-value according to t-test. N=8 per group.

Table 11: Raw data of the histogram depicted in Fig. 2. Single values represent the means from three different observers blinded with respect to treatment.

Animal	100% paraffin (formulation c)	Example 2 (formulation d)
1	2.33	1.29
2	1.77	1.78
3	1.50	0.69
4	1.91	1.34
5	2.21	0.67
6	2.06	1.00
7	2.10	0.96
8	2.54	1.51

Fig. 3: Angiography scores of vehicle (water based, formulation e) and regorafenib (example 3, formulation f) treated animals at day 21. Data are presented as mean ± SD, p-value according to t-test. N=6 per group.

Table 12: Raw data of the histogram depicted in Fig. 3. Single values represent the means from three different observers blinded with respect to treatment.

Animal	formulation e	Example 3 (formulation f)
1	1.61	1.78
2	1.78	1.60
3	1.93	1.34
4	2.27	2.00
5	1.49	0.80
6	2.10	2.20

10

B) Efficacy regarding neovascularization (neovascular area day 23):

Fig. 4: Neovascular area of vehicle (oleoyl polyethyleneglycol glycerides (Labrafil), formulation a) and regorafenib (example 1, formulation b) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

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Table 13: Raw data of the histogram depicted in Fig. 4. Single values represent the means from all six lesions.

Animal	100 % oleoyl polyethyleneglycol glycerides (formulation a)	Example 1 (formulation b)
1	134507	90562
2	70878	59819
3	84254	67222
4	86071	72584
5	93586	30455
6	69696	47866
7	103307	23991
8	98472	63033

Fig. 5: Neovascular area of vehicle (paraffin, formulation c) and regorafenib (example 2, formulation d) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

Table 14: Raw data of the histogram depicted in Fig. 5. Single values represent the means from all six lesions.

Animal	100 % paraffin (formulation c)	Example 2 (formulation d)
1	105910	62047
2	81060	70927
3	98735	84481
4	85019	80151
5	98071	70568
6	101668	59804
7	99413	63145
8	113797	91466

Fig. 6: Neovascular area of vehicle (water based, formulation e)) and regorafenib (example 3, formulation f) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=5 per group.

Table 15: Raw data of the histogram depicted in Fig. 6. Single values represent the means from all six lesions.

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Animal	formulation e	Example 3 (formulation f)
1	78759	107547
2	83420	117379
3	96239	72404
4	107654	99371
5	87960	91977

In both groups, one flatmount preparation each could not be scored due to poor tissue quality.

Results for example 1:

5 Table 16 (n=8 per group)

Formulation	A) Vascular leakage [angiography score]	B) Choroidal neovascularization lesion size [μm²]
a) 100% oleoyl polyethyleneglycol glycerides (vehicle control)	1.80 ± 0.25	92596 ± 20754
b) Regorafenib (20 mg/ml) suspension in 100% oleoyl polyethyleneglycol glycerides (example 1)	1.13 ± 0.26	56942 ± 22025
p-value	< 0.001	0.005

Results for example 2:

Table 17 (n=8 per group)

Formulation	A) Vascular leakage [angiography score]	B) Choroidal neovascularization lesion size [μm²]
c) 100 % liquid paraffin (vehicle control)	2.05 ± 0.33	97959 ± 10580
d) Regorafenib (20 mg/ml) suspension in 100 % liquid paraffin (example 2)	1.16 ± 0.39	72824 ± 11496
p-value	< 0.001	< 0.001

10 Results for example 6:

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Table 18 (n=6 per group for leakage, n=5 per group for neovascularization)

Formulation	A) Vascular leakage [angiography score]	B) Choroidal neovascularization lesion size [μm²]
e) Water-based vehicle control	1.86 ± 0.30	90806 ± 11414
f) Regorafenib (20 mg/ml) suspension in water-based vehicle (example 6)	1.62 ± 0.50	97736 ± 17027
p-value	0.330 (n.s.)	0.471 (n.s.)

Results for example 7:

Table 19 (n=8 fo vehicle, n=7 for regorafenib)

Formulation	A) Vascular leakage [angiography score]	B) Choroidal neovascularization lesion size [μm²]
m) 100% middle chain triglycerides (Miglyol, vehicle control)	1.53 ± 0.50	84971 ± 14882
n) Regorafenib (20 mg/ml) suspension in miglyol	1.40 ± 0.27	68127 ± 8954
p-value	0.567 (n.s.)	0.022

5

Results for example 8:

Table 20 (n=8 for vehicle, n=6 for regorafenib)

Formulation	A) Vascular leakage [angiography score]	B) Choroidal neovascularization lesion size [μm²]
o) 100% Oculentum simplex (vehicle control)	1.41 ± 0.41	83301 ± 9729
p) Regorafenib (20 mg/g) suspension in oculentum simplex	1.11 ± 0.36	60628 ± 17812
p-value	0.180 (n.s.)	0.010

Results for example 3, 4 and example 5:

10 Table 21 (n= 8 - 10 per group)

Formulation	A) Vascular leakage [angiography score]	B) Choroidal neovascularization lesion size [μm²]
g) liquid Paraffin 0.5% Aerosil (vehicle control), n=10	1.65 ± 0.15	78040 ± 21180
h) Regorafenib (20 mg/ml) suspension in liquid Paraffin 0.5% Aerosil (example 3), n=9 for A), n=10 for B)	1.14 ± 0.34	55364 ± 8307
i) liquid Paraffin 2% Aerosil (vehicle control), n=10	1.63 ± 0.16	82750 ± 12471
j) Regorafenib (20 mg/ml) suspension in liquid Paraffin 2% Aerosil (example 4), n=8 for A), n=10 for B)	1.11 ± 0.13	51209 ± 4463
k) liquid Paraffin 5% Aerosil (vehicle control)	1.70 ± 0.24	66389 ± 8790
l) Regorafenib (20 mg/ml) suspension in liquid Paraffin 5% Aerosil (example 5)	1.32 ± 0.19	54984 ± 9973
p-value g vs h	< 0.001	0.0055
p-value i vs j	< 0.001	< 0.001
p-value k vs l	0.001	0.014

Example 10: Ocular pharmacokinetics:

A)

At day of experiment a defined dose of the test compound (regorafenib monohydrate 20mg/ml) as
5 suspension in different vehicles is applied to each eye by the use of an Eppendorf pipet. In a period
of 24 to 96 hours after application a sequence (8-12 time points) of animals were sacrificed to get
the eyes of these animals (rats). These eyes were rinsed in 1 ml of physiological saline solution at
least 2 times and afterwards dried with a paper flies. To determine the total concentration of the test
compound in the eye it is homogenized within a defined amount of saline solution and an aliquot of
10 the homogenate is spiked with Acetonitrile to precipitate proteins in the solution. After

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centrifugation, in the supernatant the test compound and its possible known decomposition products were quantified with appropriate LC/MS-MS methods. Are the concentrations of the test compound or its possible known decomposition products to be determined in some defined compartments of the eye, the eyes are dissected into the appropriate compartments and each compartment is homogenized, handled and measured as described above.

In that way a concentration-time curve is determined; this is then used to calculate standard pharmacokinetic parameters to assess the qualification of a certain formulation (concentration maximum and half-life). The calculated standard pharmacokinetic parameters of the test compound or of the hereof released active pharmaceutical ingredient are: AUC_{norm}, C_{max}, and MRT (mean residence time).

Pharmacokinetic parameters regarding regorafenib calculated from eye concentration-time curves for equal doses but with different formulations are shown in the table below.

Table 22:

	C _{max} [mg/L]	AUC _{norm} [kg*h/L]	MRT [h]
Labrafil (example 1)	1.0	23	40
Paraffin (example 2)	1.4	28	41
Water (example 6)	1.8	5.3	28
Miglyol (example 7)	1.1	12	30
Oculentum Simplex (example 8)	1.7	4.8	28

B)

Three unanaesthetized female rabbits were administered with a defined amount (30 µL) of suspension in Paraffin in the lower lacrimal sac of each eye. Using a glass capillary over a period of 60 min, several weight controlled samples (n=8) of tear fluid were collected. The determination of the concentration of the compound in the fluid and the evaluation of the pharmacokinetic parameters is the same as described above.

Table 23:

	C _{max} [mg/L]	AUC _{norm} [kg*h/L]	MRT [h]
Paraffin (example 2)	149	99	0.6

The results show a surprisingly high residence time of the active agent in the tear fluid and on the cornea.

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Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

What is claimed is:

1. A topical ophthalmological pharmaceutical composition comprising regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof as active agent and at least one pharmaceutically acceptable vehicle wherein the composition is a suspension comprising the active agent suspended in the applicable pharmaceutically acceptable vehicle.
2. The pharmaceutical composition of claim 1 containing regorafenib monohydrate as active agent.
3. The pharmaceutical composition of any of claims 1 to 2 wherein the active agent is in a solid form.
4. The pharmaceutical composition of any of claims 1 to 3 wherein the active agent is in a crystalline form.
5. The pharmaceutical composition of any of claims 1 to 4 wherein the active agent is in a microcrystalline form.
6. The pharmaceutical composition of any of claims 1 to 5 wherein the concentration of the active agent in the pharmaceutical composition is from 0.01 to 10% by weight of the total amount of the composition.
7. The pharmaceutical composition of any of claims 1 to 6 wherein the pharmaceutically acceptable vehicle is selected from the group comprising oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, liquid paraffin, light liquid paraffin, soft paraffin (vaseline), hard paraffin, castor oil, peanut oil, sesame oil, middle chain triglycerides, cetylstearylalcohols, wool fat, glycerol, propylene glycol, polyethyleneglycols (PEG) or a mixture of those, water or a mixture thereof.
8. The pharmaceutical composition of any of claims 1 to 7 based on a non-aqueous vehicle.
9. The pharmaceutical composition of any of claims 1 to 8 based on a hydrophobic vehicle.
10. The pharmaceutical composition of any of claims 1 to 9 wherein the pharmaceutically acceptable vehicle is selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof.

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11. The pharmaceutical composition of any of claims 1 to 10 comprising further pharmaceutically acceptable excipients like stabilizers, surfactants, polymer base carriers like gelling agents, organic co-solvents, pH active components, osmotic active components and preservatives.
12. The pharmaceutical composition of claim 11 wherein the stabilizer is a hydrophobic silica.
- 5 13. The pharmaceutical composition of claim 12 comprising hydrophobic silica in an amount of 0.1 % to 10 % by weight of the total composition.
14. A process for manufacturing a pharmaceutical composition according to any of claims 1 to 13 wherein the active agent is suspended in an applicable pharmaceutically acceptable vehicle optionally in the presence of further one or more pharmaceutically acceptable excipients and
10 the suspension is homogenized.
15. The pharmaceutical composition of any of claims 1 to 13 for the use of treating or preventing an ophthalmological disorder selected from the group comprising age-related macular degeneration (AMD), choroidal neovascularization (CNV), choroidal neovascular membrane (CNVM), cystoid macula edema (CME), epi-retinal membrane (ERM) and
15 macular hole, myopia-associated choroidal neovascularisation, vascular streaks, retinal detachment, diabetic retinopathy, diabetic macular edema (DME), atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), retinal vein occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, retinitis pigmentosa, Stargardt's disease, glaucoma,
20 inflammatory conditions, cataract, refractory anomalies, ceratoconus, retinopathy of prematurity, angiogenesis in the front of the eye, corneal angiogenesis following keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.
16. The pharmaceutical composition of claim 15 for the use of treating or preventing an
25 ophthalmological disorder selected from the group comprising dry AMD, wet AMD or choroidal neovascularization (CNV).
17. Method for treating or preventing an ophthalmological disorder selected from the group comprising age-related macular degeneration (AMD), choroidal neovascularization (CNV), choroidal neovascular membrane (CNVM), cystoid macula edema (CME), epi-retinal
30 membrane (ERM) and macular hole, myopia-associated choroidal neovascularisation, vascular streaks, retinal detachment, diabetic retinopathy, diabetic macular edema (DME), atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), retinal vein occlusion, choroidal retinal vein occlusion,

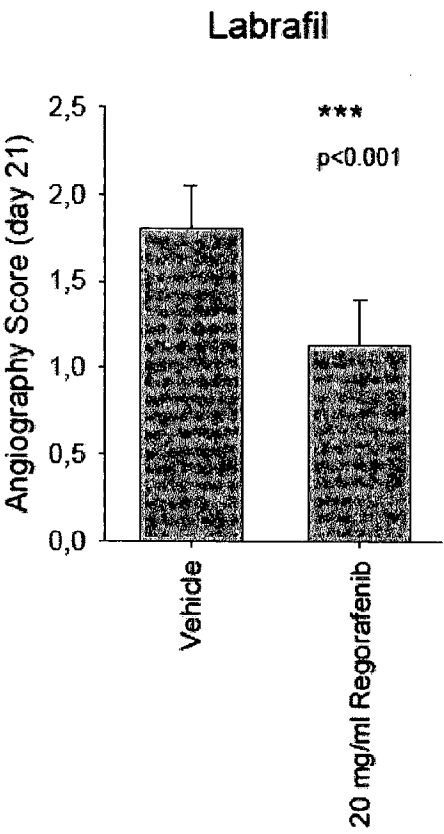
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- macular edema, macular edema due to retinal vein occlusion, retinitis pigmentosa, Stargardt's disease, glaucoma, inflammatory conditions, cataract, refractory anomalies, ceratoconus, retinopathy of prematurity, angiogenesis in the front of the eye, corneal angiogenesis following keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema comprising administering a pharmaceutical composition according to any of claims 1 to 13 containing a pharmaceutically effective amount of the active agent.
- 5
18. A topical ophthalmological pharmaceutical composition for the use of treating or preventing a posterior eye disease wherein the composition is a suspension comprising an active agent applicable for the treatment or prevention of a posterior eye disease suspended in a pharmaceutically acceptable vehicle.
- 10
19. The topical ophthalmological pharmaceutical composition of claim 18 wherein the pharmaceutically acceptable vehicle is a non-aqueous vehicle.
- 15
20. The topical ophthalmological pharmaceutical composition of claim 18 wherein the pharmaceutically acceptable vehicle is a hydrophobic vehicle.
21. The topical ophthalmological pharmaceutical composition of claim 20 wherein the pharmaceutically acceptable vehicle is selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof.

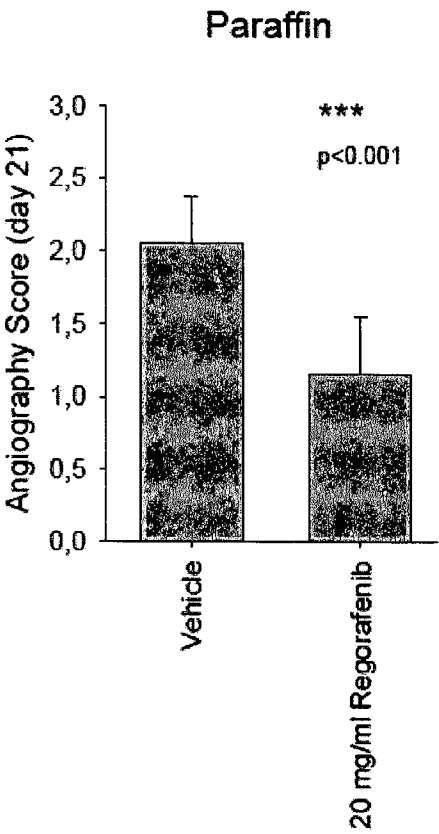
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Figure 1



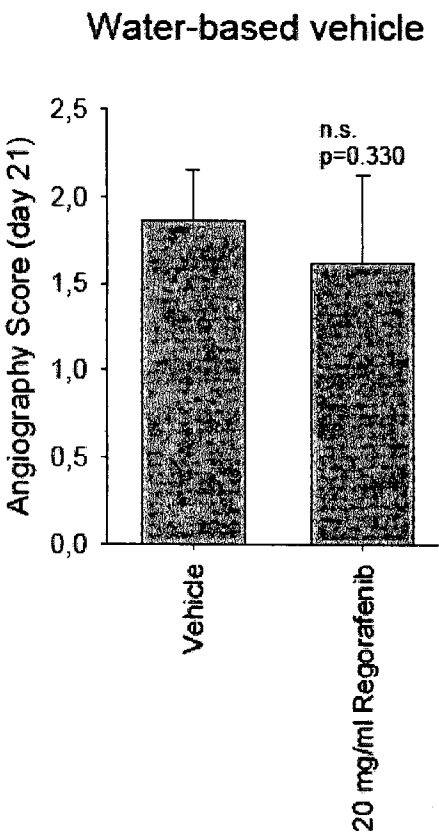
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Figure 2



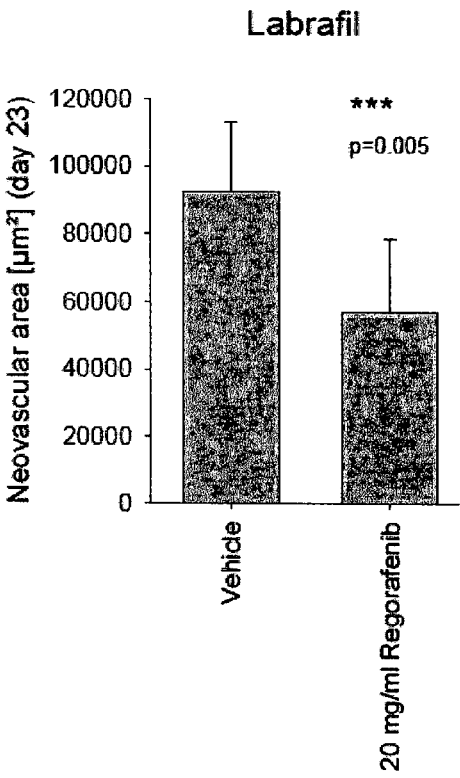
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Figure 3



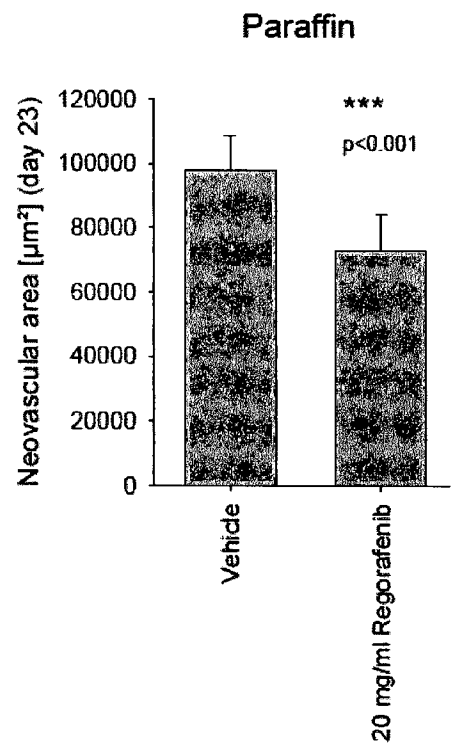
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Figure 4



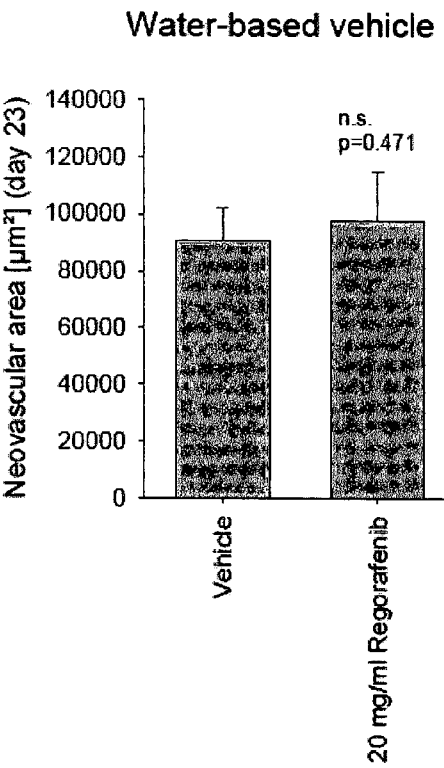
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Figure 5



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Figure 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/062365

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K9/00	A61K31/4412
ADD.	A61K47/02	A61K47/06 A61K47/14 A61K47/26 A61K47/38
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/084685 A1 (KOENEN RUEDIGER [DE] ET AL) 20 April 2006 (2006-04-20) paragraph [0086] - paragraph [0089]; example 1	18-21
X	WO 2007/068382 A1 (BAYER HEALTHCARE AG [DE]; WEBER OLAF [DE]; RIEDL BERND [DE]) 21 June 2007 (2007-06-21)	1-15, 17-21
Y	page 7, line 10 - line 29	16
Y	page 8, line 1 - line 13	
Y	US 2005/038080 A1 (BOYER STEPHEN [DE] ET AL) 17 February 2005 (2005-02-17) cited in the application the whole document paragraph [0091]	16
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance		
"E" earlier application or patent but published on or after the international filing date		
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art		
"&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
11 September 2012		19/09/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Palma, Vera

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/062365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/062365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2005009961 A2	03-02-2005

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NOTIFICATION CONCERNING SUBMISSION,
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Creative Campus Monheim, Geb. 4865
Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing (day/month/year) 30 July 2012 (30.07.2012)	
Applicant's or agent's file reference BHC111015-WO	IMPORTANT NOTIFICATION
International application No. PCT/EP2012/062365	International filing date (day/month/year) 26 June 2012 (26.06.2012)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 June 2011 (28.06.2011)
Applicant BAYER INTELLECTUAL PROPERTY GMBH et al	

The applicant is hereby notified of the date of receipt (or of obtaining by the International Bureau) of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to the date of receipt, **the priority document concerned was submitted or transmitted to or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis)**. This Form replaces any previously issued notification concerning submission, transmittal or obtaining of priority documents.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 June 2011 (28.06.2011)	11171719.5	EP	26 July 2012 (26.07.2012)
14 February 2012 (14.02.2012)	12155281.4	EP	26 July 2012 (26.07.2012)

The letters "NR" denote a priority document which, on the date of mailing of this Form, had not yet been received or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis). Where the applicant has failed to either submit, request to prepare and transmit, or to request the International Bureau to obtain the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

An asterisk "*" next to a date of receipt, denotes a priority document submitted or transmitted to or obtained by the International Bureau but not in compliance with Rule 17.1(a), (b) or (b-bis) (the priority document was received after the time limit prescribed in Rule 17.1(a); the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b) or the request to the International Bureau to obtain the priority document was made after the applicable time limit under Rule 17.1(b-bis)). Even though the priority document was not furnished in compliance with Rule 17.1(a), (b) or (b-bis), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Agnès Wittmann-Regis e-mail pt06.pct@wipo.int Telephone No. +41 22 338 74 06
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OF A CHANGE

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c/o Bayer Intellectual Property GmbH
Creative Campus Monheim
Alfred-Nobel-Strasse 10
40789 Monheim
ALLEMAGNE

Date of mailing (day/month/year)
17 December 2013 (17.12.2013)

Applicant's or agent's file reference
BHC111015-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2012/062365

International filing date (day/month/year)
26 June 2012 (26.06.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address BAYER HEALTHCARE LLC 555 White Plains Road Tarrytown, NY 10591 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address BAYER HEALTHCARE LLC 100 Bayer Boulevard Whippany, New Jersey 07981 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

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☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Buloz Isabel e-mail pt06.pct@wipo.int Telephone No. +41 22 338 74 06
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OF A CHANGE

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Creative Campus Monheim
Alfred-Nobel-Strasse 10
40789 Monheim
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Date of mailing (day/month/year) 17 December 2013 (17.12.2013)	To: ASSOCIATION BIP PATENTS c/o Bayer Intellectual Property GmbH Creative Campus Monheim Alfred-Nobel-Strasse 10 40789 Monheim ALLEMAGNE
Applicant's or agent's file reference BHC111015-WO	
International application No. PCT/EP2012/062365	IMPORTANT NOTIFICATION
	International filing date (day/month/year) 26 June 2012 (26.06.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address DEGENFELD, Georges Friedrich-Weskott-Str. 10 51373 Leverkusen Germany	State of Nationality FR	State of Residence DE
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address VON DEGENFELD, Georges Friedrich-Weskott-Str. 10 51373 Leverkusen Germany	State of Nationality FR	State of Residence DE
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Buloz Isabel
Facsimile No. +41 22 338 89 70	e-mail pt06.pct@wipo.int Telephone No. +41 22 338 74 06

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776



**DOCUMENT MADE AVAILABLE UNDER THE
PATENT COOPERATION TREATY (PCT)**

International application number:	PCT/EP2012/062365
International filing date:	26 June 2012 (26.06.2012)
Document type:	Certified copy of priority document
Document details:	Country/Office: EP
	Number: 11171719.5
	Filing date: 28 June 2011 (28.06.2011)
Date of receipt at the International Bureau:	26 July 2012 (26.07.2012)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)

111719



Bescheinigung

Die angehefteten
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Certificate

The attached documents are
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application described on the
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Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

11171719.5 / EP11171719

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP11171719.

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Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

R.C. van Dijk

ML52298

119778

Anmeldung Nr:
Application no.: 11171719.5
Demande no :

Anmeldetag:
Date of filing: 28.06.11
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

Bayer Schering Pharma Aktiengesellschaft
Müllerstrasse 178
13353 Berlin/DE

Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Topical ophthalmological pharmaceutical composition containing regorafenib

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

A61K31/00

Am Anmeldetag benannte Vertragsstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

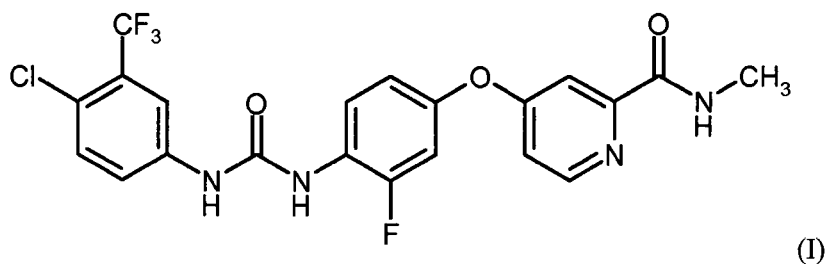
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
PT RO RS SE SI SK SM TR

1207/19

Topical Ophthalmological Pharmaceutical Composition containing Regorafenib

The present invention relates to topical ophthalmological pharmaceutical compositions containing regorafenib, a hydrate, solvate or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating ophthalmological disorders.

- 5 Regorafenib which is 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide, a compound of formula (I)



- is a potent anti-cancer and anti-angiogenic agent that possesses various activities including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signalling molecules and it can be used in treating various diseases and conditions like hyper-proliferative disorders such as cancers, tumors, lymphomas, sarcomas and leukemias as described in WO 2005/009961. Furthermore salts of the compound of formula (I) such as its hydrochloride, mesylate and phenylsulfonate are mentioned in WO 05/009961. The monohydrate of the compound of formula (I) is mentioned in WO 08/043446.

- 15 Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly population and is recognized as dry and wet AMD (Expert Opin. Ther. Patents (2010), 20(1), 103 – 11). The dry, or nonexudative, form involves both atrophic and hypertrophic changes of the retinal pigment epithelium (RPE). The dry form is characterized by macular drusen which are pigmented areas containing dead cells and metabolic products that distort the retina and eventually cause loss of acute vision. Patients with nonexudative AMD (dry form) can progress to the wet, or exudative or neovascular, AMD, in which pathologic choroidal neovascular membranes (CNVM) develop under the retina, leak fluid and blood, and, ultimately, cause a centrally blinding disciform scar over a relatively short time frame if left untreated. Choroidal neovascularization (CNV), the growth of new blood vessels from the choroid capillary network across the Bruch's membrane/RPE interface into the neural retina, results in retinal detachment, subretinal and intraretinal edema, and scarring.

Access to the choroid which is between the sclera and the retina other than via the blood is difficult. The eye is composed of three major anatomic compartments, the anterior chamber, posterior

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chamber, and vitreous cavity, that have limited physiological interaction with each other. The retina is located in the back of the vitreous cavity, and is protected from the outside by the sclera which is the white, tough, impermeable wall of the eye. Choroidal blood flow is the usual method of carrying substances to the choroid and requires e.g. oral or intravenous administration of the drug. Most drugs cannot be delivered to the choroid by eye drops or a depot in vicinity to the eye. Some drugs have been delivered to the retina and thus to the choroid by injection into the vitreous chamber of the eye.

VEGF (vascular endothelial growth factor) is a key cytokine in the development of normal blood vessels as well as the development of vessels in tumors and other tissues undergoing abnormal angiogenesis and appears to play a central role in the pathogenesis of CNV formation (Expert Opin. Ther. Patents (2010), 20(1), 103-118, Expert Opin. Ther. Patents (2009), 18(10), 1573-1580, J. Clin. Invest. (2010), 120(9), 3033-3041, J. Cell. Physiol. (2008), 216, 29-37, New Engl. J. Med. 2006, 355, 1474-1485, WO 2010/127029, WO 2007/064752). Drugs which block the effects of VEGF are described for treating wet AMD such as aptamers like pegaptanib (New Engl. J. Med. 2004, 351, 2805-2816), or VEGF antibodies like ranibizumab (New Engl. J. Med. 2006, 355, 1419-1431) or bevacizumab (Ophthalmology, 2006, 113, 363-372). However, said drugs have to be administered intravitreally by injection into the eye. Sorafenib, a VEGF inhibitor as well, is described for treating CNV by oral administration (Clinical and Experimental Ophthalmology, 2010, 38, 718-726). Pazopanib, a VEGF inhibitor as well, is described for treating AMD by topical administration of eye drops containing an aqueous solution of Pazopanib (WO 2011/009016). WO 2006/133411 describes compounds for the treatment of CNV by topical administration of liposomal formulations. WO 2007/076358, US2006257487 describe aqueous ophthalmological formulations for topical administration. WO 2008/27341 describes emulsions for topical administration to the eye.

Despite the progress described in the art there remains a need for improved medicines for the treatment of ophthalmological disorders like AMD. In particular, there remains a need for topical ophthalmological pharmaceutical compositions like eye drops which can be administered easily and therefore would increase the patient's compliance. The topical ophthalmological pharmaceutical composition has to provide a concentration of the active agent in the eye which is sufficient for an effective therapy. This is dependent on the solubility and the release behavior of the active agent. In the case of a liquid formulation the dissolution properties and chemical stability of the active agent are of importance. In order to support a high compliance the topical ophthalmological pharmaceutical composition should not have to be taken in more than 5 times a day, the less the better. Type and amount of the excipients in combination with the process of preparation of the

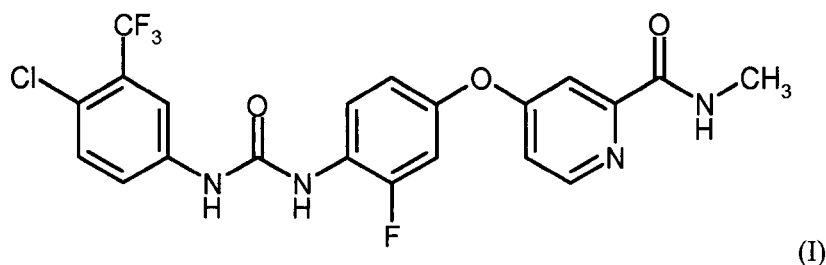
pharmaceutical composition are essential for release properties, bioavailability of the active agent in the eye, in particular in the back of the eye (e.g. in the area of the retina, Bruch's membrane and choroid), stability and the industrial applicability of the manufacturing process for the topical ophthalmological pharmaceutical composition.

- 5 The problem to be solved by the present invention is to provide a topical ophthalmological pharmaceutical composition comprising regorafenib as active agent which has a sufficient stability and which achieves an effective concentration of regorafenib in the eye, in particular in the back of the eye for the treatment of ophthalmological disorders by avoiding an intravenous or oral administration or injection into or close to the eye (e.g. intravitreal or other injections).
- 10 Regorafenib monohydrate has a limited solubility profile. The thermodynamic solubility of regorafenib monohydrate in different solvents is shown in table 1:

Table 1:

Solvent	Solubility (mg/ml)
Water	< 0.1
Paraffin	< 0.1
Ethanol	6.4
Polyethylenglycol (PEG) 400	67.3
HP β -Cyclodextrin/water (10:90)	< 0.1
PEG 400/water (30:70)	0.27
Oleoylpolyethylenglycol glycerides	3.6

- Surprisingly the pharmaceutical composition according to the invention provides by topical administration a sufficient amount of the active agent into the eye which is effective for treating ophthalmological disorders. In particular, the pharmaceutical composition according to the invention provides the active agent in a sufficient amount into the back of the eye, i.e. that the pharmaceutical composition according to the invention effects the transportation of the active agent from the front of the eye to the back of the eye. Furthermore the pharmaceutical composition according to the invention has a sufficient stability without any meaningful degradation of the active agent.
- 15
- 20 The present invention pertains to a topical ophthalmological pharmaceutical composition comprising regorafenib, the compound of the formula (I),



5 a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof and at least one pharmaceutically acceptable vehicle and optionally at least one pharmaceutically acceptable excipient.

A pharmaceutically acceptable vehicle or excipient is any vehicle or excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active agent so that any side effects ascribable to the vehicle or excipient do not vitiate the beneficial effects of the active agent.

10 The term “the compound of formula (I)” or “regorafenib” refer to 4-{4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-fluorophenoxy}-N-methylpyridine-2-carboxamide as depicted in formula (I).

The term “compound of the invention” or “active agent” refer to regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof.

15 Solvates for the purposes of the invention are those forms of the compounds or their salts where solvent molecules form a stoichiometric complex in the solid state and include, but are not limited to for example ethanol and methanol.

Hydrates are a specific form of solvates, where the solvent molecule is water. Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds or salts with water, such as, for example, hemi-, mono- or dihydrates. Preference is given to the monohydrate of
20 regorafenib.

Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic
25 acid, benzenesulfonic acid, *p*-toluenesulfonic acid (tosylate salt), 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic

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acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Preference is given to the hydrochloride, mesylate or phenylsulfonate salt of regorafenib.

- 10 Preferred are regorafenib and the monohydrate of regorafenib, most preferred is regorafenib monohydrate as compounds of the present invention.

Due to the low solubility of regorafenib, in particular of regorafenib monohydrate in aqueous and oily vehicles standard solutions are not applicable. Also solutions containing tolerable amounts of emulsifiers, solubilising agents, complex forming excipients etc. are not available.

- 15 The topical ophthalmological pharmaceutical composition according to the invention comprises the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in a solid form, preferably in a crystalline form, more preferably in a microcrystalline form.

- The minimum concentration of the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in the topical ophthalmological pharmaceutical composition is 0.1 %, preferably 0.2 % by weight of the total amount of the composition. The maximum concentration of the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in the topical ophthalmological pharmaceutical composition is 10 %, preferably 5 %, more preferably 3 % by weight of the total amount of the composition.

- 25 Preference is given to a concentration of the compound of the present invention in the pharmaceutical composition from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

Particular preference is given to a concentration of regorafenib in the pharmaceutical composition from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

- Particular preference is given to a pharmaceutical composition resulting from addition of regorafenib monohydrate in amounts from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

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The topical ophthalmological pharmaceutical composition according to the invention includes but is not limited to eye drops, gels, ointments, dispersions or suspensions.

The compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate is used preferably in a micronized form.

- 5 Micronization can be achieved by standard milling methods, preferably by air jet milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 μm , preferably from 1 to 6 μm , more preferably from 2 to 3 μm . The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).
- 10 One embodiment of the present invention is a topical ophthalmological pharmaceutical composition which is a suspension comprising the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in a solid form, preferably in a crystalline form, more preferably in a microfine crystalline form suspended in an applicable pharmaceutically acceptable vehicle, and optionally further comprising one or more pharmaceutically acceptable excipients.
- 15 Suitable pharmaceutically acceptable vehicles according to the present invention include but are not limited to oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, hydrocarbon vehicles like liquid paraffin, light liquid paraffin, soft paraffin (vaseline), hard paraffin, vegetable fatty oils like castor oil, peanut oil or sesame oil, synthetic fatty oils like middle chain triglycerides, wool alcohols like cetylstearylalcohols, wool fat, glycerol, propylene glycol,
- 20 polyethyleneglycols (PEG), water like an aqueous isotonic sodium chloride solution or a mixture of thereof, preferably oleoyl polyethyleneglycol glycerides, hydrocarbon vehicles, fatty oils or a mixture of thereof, most preferably hydrocarbon vehicles like liquid paraffin or light liquid paraffin or a mixture thereof.

- Very surprisingly the pharmaceutical composition according to the present invention comprising a
- 25 lipophilic vehicle like liquid or light liquid paraffin provides by topical administration a sufficient amount of the active agent into the eye which is effective for treating ophthalmological disorders, although the solubility of regorafenib monohydrate in lipophilic vehicles is very low.

- The pharmaceutically acceptable vehicle is the basis of the topical ophthalmological pharmaceutical composition according to the present invention and is present in the composition in a minimum
- 30 concentration of 75%, preferably 80%, more preferably 85% and in a maximum concentration of 99.9%, preferably 99%, more preferably 98% by weight of the total amount of the composition.

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Suitable further pharmaceutically acceptable excipients used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to surfactants, polymer base carriers like gelling agents, organic co-solvents, pH active components, osmotic active components and preservatives.

- 5 Suitable surfactants used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to lipids such as phospholipids, phosphatidylcholines, cardiolipins, fatty acids, phosphatidylethanolamines, phosphatides, tyloxapol, polyethyleneglycols and derivatives like PEG 400, PEG 1500, PEG 2000, poloxamer 407, poloxamer 188, polysorbate 80, polysorbate 20, sorbitan laurate, sorbitan stearate, sorbitan palmitate or a mixture thereof, preferably
- 10 polysorbate 80.

- Suitable polymer base carriers like gelling agents used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to cellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethyl cellulose (CMC), methylcellulose (MC), hydroxyethylcellulose (HEC), amylase and derivatives, amylopectins
- 15 and derivatives, dextran and derivatives, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and acrylic polymers such as derivatives of polyacrylic or polymethacrylic acid like HEMA, carbopol or a mixture thereof.

- Suitable organic co-solvents used in the pharmaceutical composition according to the invention include but are not limited to ethylene glycol, propylene glycol, N-methyl pyrrolidone, 2-pyrrolidone,
- 20 3-pyrrolidinol, 1,4-butanediol, dimethylglycol monomethylether, diethyleneglycol monomethylether, solketal, glycerol, polyethylene glycol, polypropylene glycol.

- Suitable pH active components such as buffering agents or pH-adjusting agents used in the pharmaceutical composition according to the invention include but are not limited to disodium phosphate, monosodium phosphate, boric acid, sodium borate, sodium citrate, hydrochloric acid,
- 25 sodium hydroxide.

The pH active components are chosen based on the target pH for the composition which generally ranges from pH 4 - 9.

Suitable osmotic active components used in the pharmaceutical composition according to the invention include but are not limited to sodium chloride, mannitol, glycerol.

- 30 Preservatives used in the pharmaceutical composition according to the invention include but are not limited to benzalkonium chloride, alkyl dimethylbenzylammonium chloride, cetrimide,

cetylpyridinium chloride, benzododecinium bromide, benzethonium chloride, thiomersal, chlorobutanol, benzyl alcohol, phenoxethanol, phenylethyl alcohol, sorbic acid, methyl and propyl parabens, chlorhexidine digluconate, EDTA or mixtures thereof.

Gelling agents, pH active agents and osmotic active agents are preferably used in the case of an aqueous pharmaceutically acceptable vehicle.

The amount of the suitable further pharmaceutically acceptable excipient in the suspension according to the present invention can be from 0.1 to 15 %, preferably from 0.5 to 10 %, more preferably from 1 to 5 % by the total weight of the suspension.

Preferably the amount of hydroxypropylmethylcellulose in the suspension according to the present invention can be from 0.05 to 15 %, preferably from 0.1 to 10 %, more preferably from 1 to 5 % by the total weight of the suspension.

Preferably the amount of polysorbate 80 in the suspension according to the present invention can be from 0.05 to 10 %, preferably from 0.1 to 7 %, more preferably from 0.5 to 4 % by the total weight of the suspension.

Preference is given to a topical ophthalmological pharmaceutical composition comprising crystalline regorafenib monohydrate, more preferably microcrystalline regorafenib monohydrate in a concentration of 0.1 to 10 %, more preferably 0.2 to 5 % weight of the total amount of the composition suspended in a pharmaceutically acceptable vehicle selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof.

Preference is also given to a topical ophthalmological pharmaceutical composition comprising crystalline regorafenib monohydrate, more preferably microfine crystalline regorafenib monohydrate in a concentration of 0.1 to 10 %, more preferably 0.2 to 5 % weight of the total amount of the composition suspended in oleoyl polyethyleneglycol glyceride as pharmaceutically acceptable vehicle.

The total amount of the active agent to be administered via the topical route into the eye using the pharmaceutical composition of the present invention will generally range from about 0.01 to 50 mg, preferably 0.02 to 10 mg, more preferably 0.05 to 5 mg per administration and per eye. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of ophthalmological disorders, by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art.

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The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

The pharmaceutical composition according to the invention is administered one or more, preferably up to 5, more preferably up to 3 times per day.

The typical method of administration of the pharmaceutical composition according to the invention is the topical delivery into the eye.

10 Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on individual response to the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses
15 over the day.

This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by preferably topical administration into the eye to a patient in need thereof, and will have advantageous properties in terms of drug release, bioavailability, and/or compliance in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular
20 condition or disease.

The pharmaceutical composition according to the invention is chemically stable for more than 18 months, preferably more than 24 months. Chemically stable according the present invention means that the active agent does not degrade significantly ($< 0.6\%$) during storage.

In other words the topical ophthalmological pharmaceutical composition according to the invention
25 contains 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide in an amount of equal or less than 0.05%, that means from 0.0001% to a maximum of 0.05%, preferably in an amount of equal or less than 0.025%, that means from 0.0001% to a maximum of 0.025%, most preferably in an amount of equal or less than 0.01%, that means from 0.0001% to a maximum of 0.01% by weight based on the amount of the compound of the formula (I).

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728Process for manufacturing

Various methods can be used to prepare the ophthalmological pharmaceutical composition according to the invention. First the pharmaceutically acceptable vehicle is prepared by optionally mixing the applicable vehicle or mixture of vehicles with the pharmaceutically acceptable excipients. Thereafter the active agent is dispersed or suspended into said mixture. The process may also include sterilization e.g. by sterile precipitation, gamma irradiation, sterile filtration, heat sterilization, aseptic filling, or a combination of such optional steps.

The present invention also relates to a process for the manufacturing of a topical ophthalmological pharmaceutical composition according to the invention, wherein the compound of the present invention is suspended in an applicable pharmaceutically acceptable vehicle optionally in the presence of further one or more pharmaceutically acceptable excipients and the suspension is homogenized.

Preference is given to a process for the manufacturing of a topical ophthalmological pharmaceutical composition according to the invention, wherein

- a) the applicable pharmaceutically acceptable vehicle or a mixture of applicable pharmaceutically acceptable vehicles is prepared by mixing the vehicles optionally in the presence of a further one or more pharmaceutically acceptable excipients,
 - b) the compound of the present invention, preferably regorafenib, more preferably regorafenib monohydrate, is suspended into said applicable pharmaceutically acceptable vehicle for example at room temperature, optionally in the presence of a further one or more pharmaceutically acceptable excipients,
 - c) the suspension is homogenized by stirring, shaking or vortexing, preferably stirring, at room temperature,
 - d) the suspension is subdivided into single units and filled into applicable vials, container, tube, flask, dropper and/or syringe.
- Optionally in step a) the further one or more pharmaceutically acceptable excipients are added to the applicable pharmaceutically acceptable vehicle at elevated temperatures for example of 40 to 70°C.

Method of treating ophthalmological disorders

The present invention also relates to a use of the pharmaceutical composition according to the invention to treat or prevent ophthalmological disorders.

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Examples of ophthalmological disorders according to the invention include but are not limited to age-related macular degeneration (AMD), choroidal neovascularization (CNV), retinal detachment, diabetic retinopathy, atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), diabetic macular edema, retinal vein occlusion, choroidal
5 retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, angiogenesis in the front of the eye like corneal angiogenesis following e.g. keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.

Examples of age-related macular degeneration (AMD) include but are not limited to dry or
10 nonexudative AMD, or wet or exudative or neovascular AMD.

Preference is given to age-related macular degeneration (AMD) like dry AMD, wet AMD or choroidal neovascularization (CNV).

The pharmaceutical composition according to the invention can be administered as the sole pharmaceutical composition or in combination with one or more other pharmaceutical compositions or active agents where
15 the combination causes no unacceptable adverse effects.

“Combination” means for the purposes of the invention not only a dosage form which contains all the active agents (so-called fixed combinations), and combination packs containing the active agents separate from one another, but also active agents which are administered simultaneously or sequentially, as long as they are employed for the prophylaxis or treatment of the same disease.

20 Since the combination according to the invention is well tolerated and is potentially effective even in low dosages, a wide range of formulation variants is possible. Thus, one possibility is to formulate the individual active ingredients of the combination according to the invention separately. In this case, it is not absolutely necessary for the individual active ingredients to be taken at the same time; on the contrary, sequential intake may be advantageous to achieve optimal effects. It is appropriate
25 with such separate administration to combine the formulations of the individual active ingredients simultaneously together in a suitable primary packaging. The active ingredients are present in the primary packaging in each case in separate containers which may be, for example, tubes, bottles or blister packs. Such separate packaging of the components in the joint primary packaging is also referred to as a kit.

30 In one embodiment, the pharmaceutical compositions of the present invention can be combined with other ophthalmological agents. Examples of such agents include but are not limited to carotenoids like lycopene,

lutein, zeaxanthin, phytoene, phytofluene, carnosic acid and derivatives thereof like carnosol, 6,7-dehydrocarnosic acid, 7-ketocarnosic acid, a zinc source like zinc oxide or a zinc salt like its chloride, acetate, gluconate, carbonate, sulphate, borate, nitrate or silicate salt, copper oxide, vitamin A, vitamin C, vitamin E and/or β -carotene.

- 5 In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors targeting receptor kinases of the domain families of e.g. VEGFR, PDGFR, FGFR and their respective ligands or other pathway inhibitors like VEGF-Trap (aflibercept), pegaptanib, ranibizumab, pazopanib, bevasiranib, KH-902, mecamlamine, PF-04523655, E-10030, ACU-4429, volociximab, sirolimus, fenretinide, disulfiram, sonepcizumab and/or tandospirone. These
- 10 agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans,
- 15 March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood
- 20 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539), PKC412, nepafenac.

Preference is given to a combination with bevacizumab, aflibercept, pegaptanib, ranibizumab, pazopanib and/or bevasiranib.

- Generally, the use of the other ophthalmological agents in combination with the pharmaceutical
- 25 compositions of the present invention will serve to:

- (1) yield better efficacy as compared to administration of either agent alone,
- (2) provide for the administration of lesser amounts of the administered agents,
- (3) provide for treating a broader spectrum of mammals, especially humans,
- (4) provide for a higher response rate among treated patients,

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(5) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other agent combinations produce antagonistic effects. It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

- 5 It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

All publications, applications and patents cited above and below are incorporated herein by reference.

The weight data are, unless stated otherwise, percentages by weight and parts are parts by weight.

10 **Examples:**

HPLC Methods:

- Two separate HPLC methods were developed for the determination of regorafenib content, unidentified degradation products and unidentified secondary components, as well as for the determination of the specific degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA), respectively, within pharmaceutical formulations.
- 15

- 1) HPLC method for the determination of regorafenib content, unidentified secondary components, and unidentified degradation products: Samples were prepared by dilution of drawn formulation aliquots with water/acetonitrile (25/75) to a final regorafenib concentration of 100µg/ml. 10µl of each sample were injected into an Agilent 1100 HPLC system (Agilent, Waldbronn, Germany), and
- 20 samples were run on a heated (40°C) Symmetry C18 column (150 x 4,6mm - 3,5µm particle size, Waters, Eschborn, Germany) applying a flow rate of 1ml/min. The mobile phase consisted of a mixture of potassium phosphate buffer pH 2.4 (A) and acetonitrile/ethanol (6/4) (B). The following gradient was applied: minute 0: A, 60% / B, 40%; minute 12: A, 20% / B, 80%; minute 16: A, 20% / B, 80%; minute 16.5: A, 60% / B, 40%; minute 20: A, 60% / B, 40%. Regorafenib, unidentified
- 25 secondary components, and unidentified degradation products were quantified using a DAD detector at a wavelength of 265 nm. Regorafenib content (column 3 in tables below) within formulations was quantified by using an external 2-point calibration straight line. Unidentified secondary components and unidentified degradation products (columns 5-7 in tables below) are described as % of summarized sample-related peak areas. Precision of the system was determined with each sample set
- 30 run, by six times injection of a 100% regorafenib standard (e.g. 100µg/ml), coefficient of variation

of peak areas resulting from these six injections was always below 2%. Relative Y-axis intercept of a 2-point (e.g. 50µg/ml, 100µg/ml) calibration straight line was always below 3% (referring to 100% Regorafenib standard). The regorafenib peak appears at 11.5 minutes.

2) HPLC method for the determination of the specific degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA). Samples were prepared by dilution of drawn formulation aliquots with acetone to a final regorafenib concentration of 3000µg/ml. 15µl of each sample were injected into an Agilent 1100 HPLC system (Agilent, Waldbronn, Germany), and samples kept at 10° in the autosampler were run on a Symmetry C18 column (150 x 4,6mm - 3,5µm particle size, Waters, Eschborn, Germany) held at 20°C with a flow rate of 1ml/min. The mobile phase consisted of a mixture of potassium phosphate buffer pH 2.4 (A) and acetonitrile/ethanol (6/4) (B). The following gradient was applied: minute 0: A, 62% / B, 38%; minute 5: A, 44% / B, 56%; minute 5.01: A, 15% / B, 85%; minute 9: A, 15% / B, 85%; minute 9.01: A, 62% / B, 38%; minute 12: A, 62% / B, 38%. 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (column 4 in tables below) was quantified using a DAD detector at a wavelength of 232 nm, referring to an external 3-point (e.g. 0.04µg/ml, 0.1µg/ml, 1µg/ml) calibration straight line. The 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide peak appears at 3.9 minutes. Limit of detection (LOD) and limit of quantification (LOQ) of 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide were determined for two different matrices (water and paraffin), and were: LOD: 4ppm (water), 13ppm (paraffin); LOQ: 13ppm (water) and 43ppm (paraffin).

Example 1: Ophthalmological suspension comprising regorafenib monohydrate in oleoyl polyethyleneglycol glyceride (20 mg/ml)

200 mg of micronized regorafenib monohydrate was suspended in oleoyl polyethyleneglycol glyceride (10 ml). The suspension was homogenized by stirring at room temperature for 15 minutes.

Stability of regorafenib in oleoyl polyethyleneglycol glyceride was tested at a concentration of 3 mg/ml over 4 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 95.0-101% of theoretical concentration, largest unidentified degradation product ranged from 0.3 to 0.7%. 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA) content was below < 13 ppm (< LOD determined for paraffin based formulation, Table 2). For analytical details see HPLC Method section above.

Table 2. Content and stability of regorafenib within oleoyl polyethyleneglycol glyceride based formulation:

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1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (ppm referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		95.0	< 13	0.04	0.04	0.7
1 day	25°C / 60% r.h.	101	< 13	0.04	0.04	0.6
4 weeks	25°C / 60%r.h.	99.0	< 13	0.04	0.04	0.3
4weeks	40°C / 75%r.h.	98.7	< 13	0.04	0.04	0.3

Example 2: Ophthalmological suspension comprising regorafenib monohydrate in liquid paraffin (20 mg/ml)

400 mg of micronized regorafenib monohydrate was suspended in 20 ml of light liquid paraffin. The suspension was homogenized by stirring at room temperature for 15 minutes.

Stability of the suspension was tested at a concentration of 20mg/ml over 13 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 74.8-99.6% of theoretical concentration. The observed fluctuation is most likely due to inhomogeneity of the sample after manual shaking of the suspension. No unidentified degradation product was observed in chromatograms. AFP-PMA content was below < 43 ppm (< LOQ determined for paraffin based formulation, Table 3). For analytical details see Analytics section above.

Table 3. Content and stability of regorafenib within paraffin based formulation.

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1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (ppm referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		99.6	< 43	0.04	0.04	-
4 weeks	25°C/60 %r.h.	85.4	< 43	0.04	0.04	-
4 weeks	40°C/75 %r.h.	74.8	< 43	0.04	0.04	-
13 weeks	25°C/60 %r.h.	96.9	< 43	0.04	0.04	-
13 weeks	40°C/75 %r.h.	94.6	< 43	0.04	0.04	-

Example 3: Ophthalmological suspension comprising regorafenib monohydrate in water based vehicle (20 mg/ml)

- 1.7 g of hydroxypropymethylcellulose 15 cp (HPMC) was dispersed in isotonic sodium chloride solution (48 g, 0.9% NaCl in water) at 70°C. The mixture was cooled down to room temperature while stirring. At room temperature evaporated water, and subsequently polysorbate 80 (0.5 g) was added and dissolved under moderate stirring. 518 mg of regorafenib monohydrate was added to an aliquot of the prepared vehicle (24.5g) and the suspension was homogenized by gently stirring at room temperature for 15 minutes.
- Stability of the suspension was tested at a concentration of 10 mg/ml over 13 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 103-112% of

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theoretical concentration. The observed fluctuation is most likely due to inhomogeneity of the sample after manual shaking of the suspension. Largest unidentified degradation product was < 0.1% of summarized sample related peak areas. Amount of AFP-PMA was determined only after 9 weeks storage.

5 Table 4. Content and Stability of Regorafenib within water based formulation.

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (ppm referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		103	n.d.	0.04	0.04	-
4 weeks	25°C/60 %r.h.	104	n.d.	0.1	0.04	-
4 weeks	40°C/75 %r.h.	112	n.d.	0.1	0.04	-
9 weeks	25°C/60 %r.h.		56			
9 weeks	40°C/75 %r.h.		86			
13 weeks	25°C/60 %r.h.	104	n.d.	0.06	0.04	-
13 weeks	40°C/75 %r.h.	104	n.d.	0.06	0.04	-

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In tables 2, 3 and 4 above column 5 describes the percental amount of the largest unidentified secondary component in the standard used in the HPLC method to be compared with the value of column 6 which describes the percental amount of the same unidentified secondary component in the formulation. Column 7 describes the percental amount of the largest unidentified degradation product in the formulation which is not AFP-PMA. Said degradation product is not detectable in the standard but is formed in the formulation.

Example 4: Topical efficacy of different formulations containing regorafenib in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether twice daily topical administration (eye drops) of the topical ophthalmological pharmaceutical compositions according to the invention results in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation (Dobi et al, Arch. Ophthalmol. 1989, 107(2), 264-269 or Frank et al, Curr. Eye Res. 1989 Mar, 8(3), 239-247)

For this purpose, a total of 44 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly assigned to eight groups of six to eight animals each. On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg / kg xylazine and 80 mg / kg ketamine (dissolved in water containing 5 mg/ml chlorobutanol hemihydrate and propylenglycol) After instillation of one drop of 0.5 % atropin (dissolved in 0.9 % saline containing Benzalkoniumchloride) to dilate the pupils, choroidal neovascularisation was induced by burning six holes in the retina (disruption of Bruch's membrane) of one eye per animal (lesion size: 50 µm, laser intensity: 150 mW; stimulus duration: 100 ms) using a 532 nm argon laser.

The following formulations were included:

- a) 100 % oleoyl polyethyleneglycol glycerides as used in example 1 (vehicle control), n=8
- b) Example 1 (20 mg/ml, suspension), n=8
- 25 c) 100 % light liquid paraffin as used in example 2 (vehicle control), n=8
- d) Example 2 (20 mg/ml, suspension), n=8
- e) Water-based vehicle (Hydroxypropymethylcellulose 15 cp 3.5%, polysorbate 80 0.5%, isotonic NaCl solution 96% (vehicle control), n=6
- f) Example 3 (20 mg/ml, suspension), n=6

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Of each formulation, 10 µl were applied to the affected eye twice daily at an 10:14 hour interval during the complete observation period of 23 days. The body weight of all animals was recorded before the start and once daily during the study. An angiography was performed on day 21 using a fluorescence fundus camera (Kowe Genesis Df, Japan). Here, after anesthesia and pupillary dilation, 10 % sodium fluorescein (dye, dissolved in water) was subcutaneously injected and pictures were recorded 2 and 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by three different examiners who were blinded for group allocation (examples 1 to 3 versus respective vehicle). Each lesion was scored with 0 (no leakage) to 3 (strongly stained), and a mean from all 6 lesions was used as the value for the respective animal. On day 23, animals were sacrificed and eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, and the sclera-choroid complex was washed, blocked and stained with a FITC-isolectine B4 antibody in order to visualize the vasculature. Then, the sclera-choroids were flat-mounted and examined under a fluorescence microscope (Keyence Biozero) at 488 nm excitation wavelength. The area (in µm²) of choroidal neovascularization was measured using ImageTool software.

Results:

A) Efficacy regarding vascular leakage (angiography scores day 21):

Fig. 1: Angiography scores of vehicle (oleoyl polyethyleneglycol glycerides (Labrafil), formulation a) and regorafenib (example 1, formulation b) treated animals at day 21. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

Table 5: Raw data of the histogram depicted in Fig. 1. Single values represent the means from three different observers blinded with respect to treatment.

Animal	100% oleoyl polyethyleneglycol glycerides (formulation a)	Example 1 (formulation b)
1	1,80	1,14
2	1,72	0,67
3	1,63	1,44
4	1,72	0,90
5	1,67	1,00
6	2,00	1,22

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7	1,56	1,33
8	2,33	1,33

Fig. 2: Angiography scores of vehicle (paraffin, formulation c) and regorafenib (example 2, formulation d) treated animals at day 21. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

5 Table 6: Raw data of the histogram depicted in Fig. 2. Single values represent the means from three different observers blinded with respect to treatment.

Animal	100% paraffin (formulation c)	Example 2 (formulation d)
1	2,33	1,29
2	1,77	1,78
3	1,50	0,69
4	1,91	1,34
5	2,21	0,67
6	2,06	1,00
7	2,10	0,96
8	2,54	1,51

Fig. 3: Angiography scores of vehicle (water based, formulation e) and regorafenib (example 3, formulation f) treated animals at day 21. Data are presented as mean ± SD, p-value according to t-test. N=6 per group.

10

Table 7: Raw data of the histogram depicted in Fig. 3. Single values represent the means from three different observers blinded with respect to treatment.

Animal	formulation e	Example 3 (formulation f)
1	1,61	1,78
2	1,78	1,60
3	1,93	1,34
4	2,27	2,00
5	1,49	0,80
6	2,10	2,20

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B) Efficacy regarding neovascularization (neovascular area day 23):

Fig. 4: Neovascular area of vehicle (oleoyl polyethyleneglycol glycerides (Labrafil), formulation a) and regorafenib (example 1, formulation b) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

Table 8: Raw data of the histogram depicted in Fig. 4. Single values represent the means from all six lesions.

Animal	100 % oleoyl polyethyleneglycol glycerides (formulation a)	Example 1 (formulation b)
1	134507	90562
2	70878	59819
3	84254	67222
4	86071	72584
5	93586	30455
6	69696	47866
7	103307	23991
8	98472	63033

Fig. 5: Neovascular area of vehicle (paraffin, formulation c) and regorafenib (example 2, formulation d) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

Table 9: Raw data of the histogram depicted in Fig. 5. Single values represent the means from all six lesions.

Animal	100 % paraffin (formulation c)	Example 2 (formulation d)
1	105910	62047
2	81060	70927
3	98735	84481
4	85019	80151
5	98071	70568
6	101668	59804

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7	99413	63145
8	113797	91466

Fig. 6: Neovascular area of vehicle (water based, formulation e)) and regorafenib (example 3, formulation f) treated animals at day 23. Data are presented as mean $\pm$ SD, p-value according to t-test. N=5 per group.

5

Table 10: Raw data of the histogram depicted in Fig. 6. Single values represent the means from all six lesions.

Animal	formulation e	Example 3 (formulation f)
1	78759	107547
2	83420	117379
3	96239	72404
4	107654	99371
5	87960	91977

In both groups, one flatmount preparation each could not be scored due to poor tissue quality.

10 Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

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102**What is claimed is:**

1. A topical ophthalmological pharmaceutical composition comprising regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof as active agent and at least one pharmaceutically acceptable vehicle.
- 5 2. The pharmaceutical composition of claim 1 containing regorafenib monohydrate as active agent.
3. The pharmaceutical composition of any of claims 1 to 2 wherein the active agent is in a solid form.
4. The pharmaceutical composition of any of claims 1 to 3 wherein the active agent is in a crystalline form.
- 10 5. The pharmaceutical composition of any of claims 1 to 4 wherein the active agent is in a microcrystalline form.
6. The pharmaceutical composition of any of claims 1 to 5 wherein the concentration of the active agent in the pharmaceutical composition is from 0.1 to 10% by weight of the total amount of the composition.
- 15 7. The pharmaceutical composition of any of claims 1 to 5 wherein the concentration of the active agent in the pharmaceutical composition is from 0.1 to 100 mg/ml.
8. The pharmaceutical composition of any of claims 1 to 5 in form of eye drops, gels, ointments, dispersions or suspensions.
9. The pharmaceutical composition of any of claims 1 to 5 which is a suspension comprising the
20 active agent suspended in an applicable pharmaceutically acceptable vehicle.
10. The pharmaceutical composition of claim 9 wherein the pharmaceutically acceptable vehicle is selected from the group comprising oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, liquid paraffin, light liquid paraffin, soft paraffin (vaseline), hard paraffin, castor oil, peanut oil, sesame oil, middle chain
25 triglycerides, cetylstearylalcohols, wool fat, glycerol, propylene glycol, polyethyleneglycols (PEG) or a mixture of those, water or a mixture thereof.
11. The pharmaceutical composition of claim 10 wherein the pharmaceutically acceptable vehicle is selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof.

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12. A combination comprising the pharmaceutical composition according to any of claims 1 to 12 combined with one or more further active agents.
13. A process for manufacturing a pharmaceutical composition according to any of claims 1 to 12 wherein the active agent is suspended in an applicable pharmaceutically acceptable vehicle optionally in the presence of further one or more pharmaceutically acceptable excipients and the suspension is homogenized.
14. The pharmaceutical composition of any of claims 1 to 12 for the use of treating or preventing an ophthalmological disorder selected from the group comprising age-related macular degeneration (AMD), choroidal neovascularization (CNV), retinal detachment, diabetic retinopathy, atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), diabetic macular edema, retinal vein occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, angiogenesis in the front of the eye, corneal angiogenesis following keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.
15. The pharmaceutical composition of claim 14 for the use of treating or preventing an ophthalmological disorder selected from the group comprising dry AMD, wet AMD or choroidal neovascularization (CNV).
16. Method for using the pharmaceutical composition according to any of claims 1 to 12 to treat or prevent an ophthalmological disorder selected from the group comprising age-related macular degeneration (AMD), choroidal neovascularization (CNV), retinal detachment, diabetic retinopathy, atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), diabetic macular edema, retinal vein occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, angiogenesis in the front of the eye, corneal angiogenesis following keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.

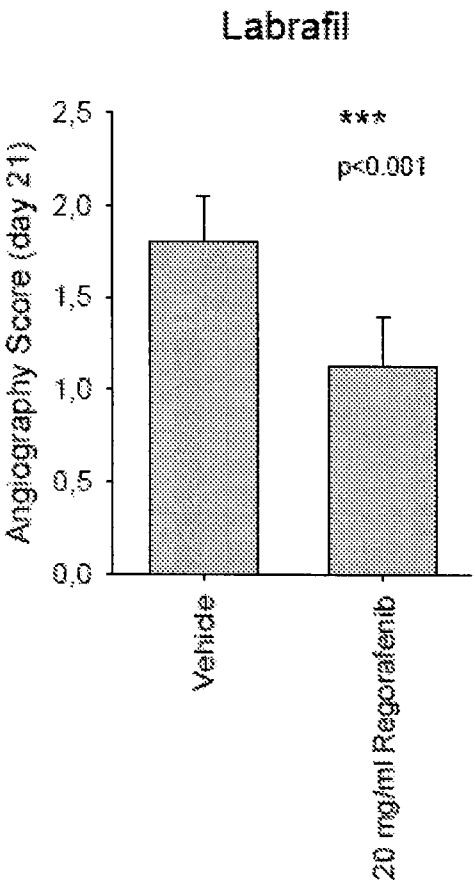
Topical Ophthalmological Composition containing Regorafenib

A b s t r a c t

The present invention relates to topical ophthalmological pharmaceutical compositions containing regorafenib, a hydrate, solvate or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating ophthalmological disorders.

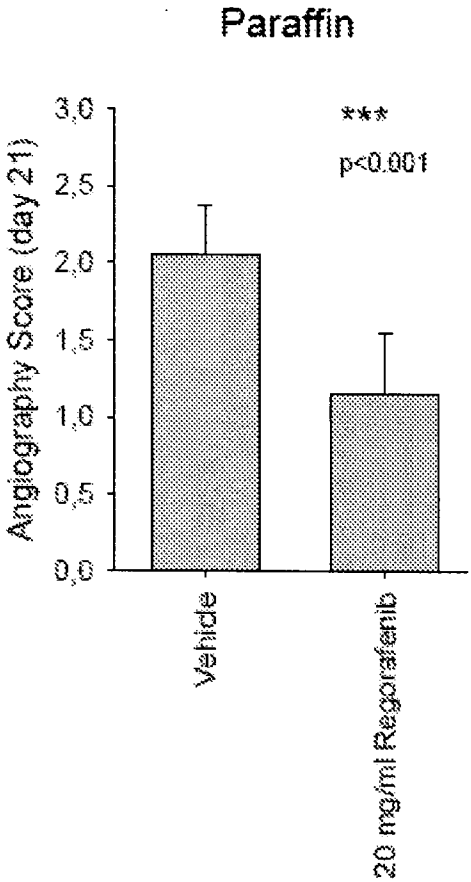
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Figure 1



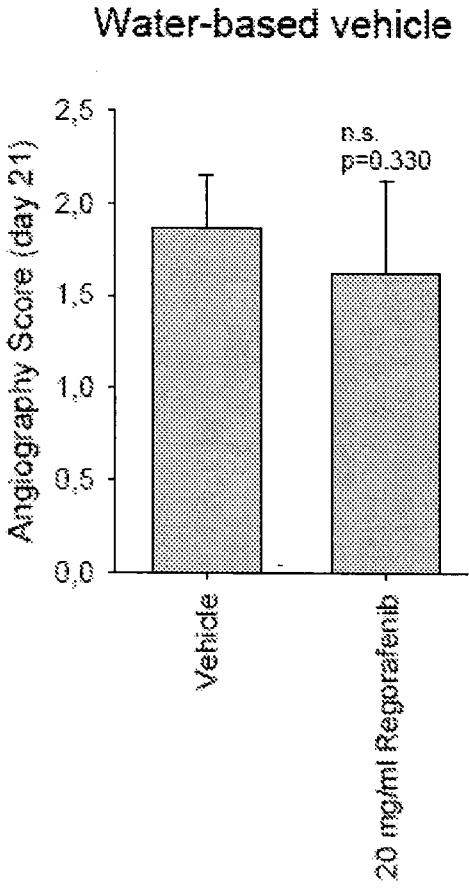
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Figure 2



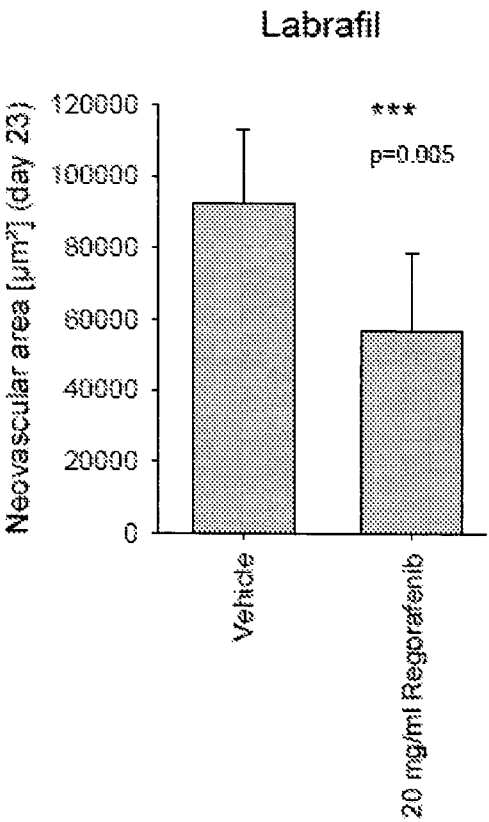
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Figure 3



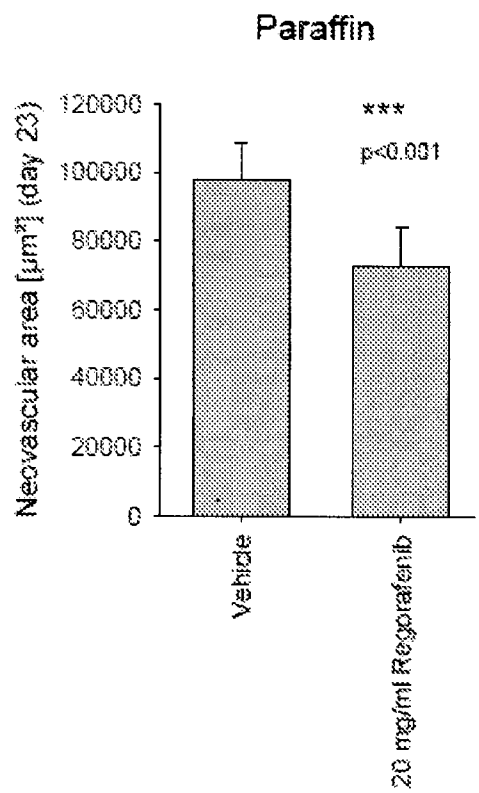
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Figure 4



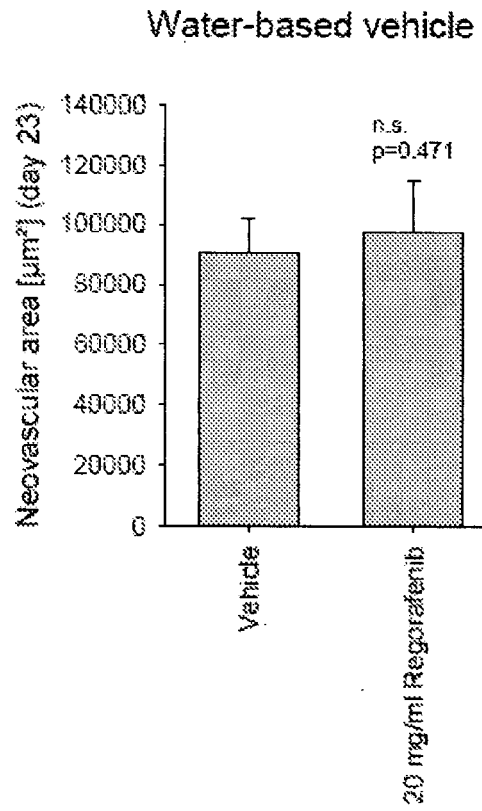
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Figure 5



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Figure 6



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U. Ingmann

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Müllerstrasse 178
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Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Topical Ophthalmological Pharmaceutical Composition containing Regorafenib

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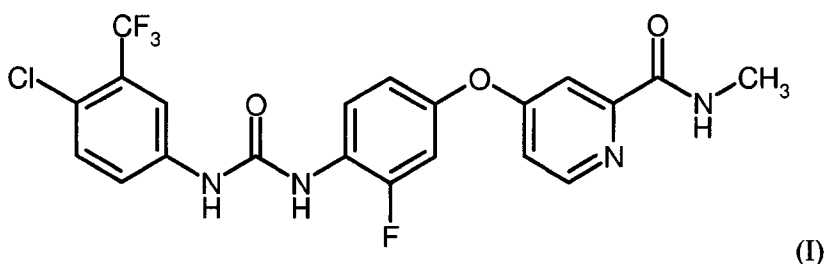
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Topical Ophthalmological Pharmaceutical Composition containing Regorafenib

The present invention relates to topical ophthalmological pharmaceutical compositions containing regorafenib, a hydrate, solvate or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating ophthalmological disorders.

- 5 Regorafenib which is 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide, a compound of formula (I)



- 10 is a potent anti-cancer and anti-angiogenic agent that possesses various activities including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signalling molecules and it can be used in treating various diseases and conditions like hyper-proliferative disorders such as cancers, tumors, lymphomas, sarcomas and leukemias as described in WO 2005/009961. Furthermore salts of the compound of formula (I) such as its hydrochloride, mesylate and phenylsulfonate are mentioned in WO 05/009961. The monohydrate of the compound of formula (I) is mentioned in WO 08/043446.

- 15 Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly population and is recognized as dry and wet AMD (Expert Opin. Ther. Patents (2010), 20(1), 103 – 11). The dry, or nonexudative, form involves both atrophic and hypertrophic changes of the retinal pigment epithelium (RPE). The dry form is characterized by macular drusen which are pigmented areas containing dead cells and metabolic products that distort the retina and eventually cause loss of acute vision. Patients with nonexudative AMD (dry form) can progress to the wet, or exudative or neovascular, AMD, in which
20 pathologic choroidal neovascular membranes (CNVM) develop under the retina, leak fluid and blood, and, ultimately, cause a centrally blinding disciform scar over a relatively short time frame if left untreated. Choroidal neovascularization (CNV), the growth of new blood vessels from the choroid capillary network across the Bruch's membrane/RPE interface into the neural retina, results in retinal detachment, subretinal and intraretinal edema, and scarring.

- 25 Access to the choroid which is between the sclera and the retina other than via the blood is difficult. The eye is composed of three major anatomic compartments, the anterior chamber, posterior chamber, and vitreous cavity, that have limited physiological interaction with each other. The retina is located in the back of the vitreous cavity, and is protected from the outside by the sclera which is the white, tough,

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impermeable wall of the eye. Choroidal blood flow is the usual method of carrying substances to the choroid and requires e.g. oral or intravenous administration of the drug. Most drugs cannot be delivered to the choroid by eye drops or a depot in vicinity to the eye. Some drugs have been delivered to the retina and thus to the choroid by injection into the vitreous chamber of the eye.

5 VEGF (vascular endothelial growth factor) is a key cytokine in the development of normal blood vessels as well as the development of vessels in tumors and other tissues undergoing abnormal angiogenesis and appears to play a central role in the pathogenesis of CNV formation (Expert Opin. Ther. Patents (2010), 20(1), 103-118, Expert Opin. Ther. Patents (2009), 18(10), 1573-1580, J. Clin. Invest. (2010), 120(9), 3033-3041, J. Cell. Physiol. (2008), 216, 29-37, New Engl. J. Med. 2006, 355, 1474-1485, WO
10 2010/127029, WO 2007/064752). Drugs which block the effects of VEGF are described for treating wet AMD such as aptamers like pegaptanib (New Engl. J. Med. 2004, 351, 2805-2816), or VEGF antibodies like ranibizumab (New Engl. J. Med. 2006, 355, 1419-1431) or bevacizumab (Ophthalmology, 2006, 113, 363-372). However, said drugs have to be administered intravitreally by injection into the eye. Sorafenib, a VEGF inhibitor as well, is described for treating CNV by oral administration (Clinical and
15 Experimental Ophthalmology, 2010, 38, 718-726). Pazopanib, a VEGF inhibitor as well, is described for treating AMD by topical administration of eye drops containing an aqueous solution of Pazopanib (WO 2011/009016). WO 2006/133411 describes compounds for the treatment of CNV by topical administration of liposomal formulations. WO 2007/076358, US2006257487 describe aqueous ophthalmological formulations for topical administration. WO 2008/27341 describes emulsions for
20 topical administration to the eye.

Despite the progress described in the art there remains a need for improved medicines for the treatment of ophthalmological disorders like AMD. In particular, there remains a need for topical ophthalmological pharmaceutical compositions like eye drops which can be administered easily and therefore would increase the patient's compliance. The topical ophthalmological pharmaceutical composition has to
25 provide a concentration of the active agent in the eye which is sufficient for an effective therapy. This is dependent on the solubility and the release behavior of the active agent. In the case of a liquid formulation the dissolution properties and chemical stability of the active agent are of importance. In order to support a high compliance the topical ophthalmological pharmaceutical composition should not have to be taken in more than 5 times a day, the less the better. Type and amount of the excipients in
30 combination with the process of preparation of the pharmaceutical composition are essential for release properties, bioavailability of the active agent in the eye, in particular in the back of the eye (e.g. in the area of the retina, Bruch's membrane and choroid), stability and the industrial applicability of the manufacturing process for the topical ophthalmological pharmaceutical composition.

The problem to be solved by the present invention is to provide a topical ophthalmological
35 pharmaceutical composition comprising regorafenib as active agent which has a sufficient stability and

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which achieves an effective concentration of regorafenib in the eye, in particular in the back of the eye for the treatment of ophthalmological disorders by avoiding an intravenous or oral administration or injection into or close to the eye (e.g. intravitreal or other injections).

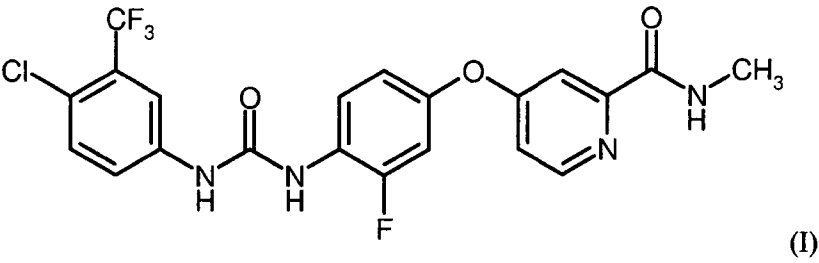
Regorafenib monohydrate has a limited solubility profile. The thermodynamic solubility of regorafenib monohydrate in different solvents is shown in table 1:

Table 1:

Solvent	Solubility (mg/ml)
Water	< 0.1
Paraffin	< 0.1
Ethanol	6.4
Polyethylenglycol (PEG) 400	67.3
HPβ-Cyclodextrin/water (10:90)	< 0.1
PEG 400/water (30:70)	0.27
Oleoylpolyethylenglycol glycerides	3.6

Surprisingly the pharmaceutical composition according to the invention provides by topical administration a sufficient amount of the active agent into the eye which is effective for treating ophthalmological disorders. In particular, the pharmaceutical composition according to the invention provides the active agent in a sufficient amount into the back of the eye, i.e. that the pharmaceutical composition according to the invention effects the transportation of the active agent from the front of the eye to the back of the eye. Furthermore the pharmaceutical composition according to the invention has a sufficient stability without any meaningful degradation of the active agent.

The present invention pertains to a topical ophthalmological pharmaceutical composition comprising regorafenib, the compound of the formula (I),



a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof and at least one pharmaceutically acceptable vehicle and optionally at least one pharmaceutically acceptable excipient.

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A pharmaceutically acceptable vehicle or excipient is any vehicle or excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active agent so that any side effects ascribable to the vehicle or excipient do not vitiate the beneficial effects of the active agent.

5 The term "the compound of formula (I)" or "regorafenib" refer to 4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl}amino]-3-fluorophenoxy}-N-methylpyridine-2-carboxamide as depicted in formula (I).

The term "compound of the invention" or "active agent" refer to regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof.

10 Solvates for the purposes of the invention are those forms of the compounds or their salts where solvent molecules form a stoichiometric complex in the solid state and include, but are not limited to for example ethanol and methanol.

Hydrates are a specific form of solvates, where the solvent molecule is water. Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds or salts with water, such as, for example, hemi-, mono- or dihydrates. Preference is given to the monohydrate of regorafenib.

15 Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid (tosylate salt), 1-naphthalenesulfonic acid, 2-
20 naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted
25 ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Preference is given to the hydrochloride, mesylate or phenylsulfonate salt of regorafenib.

30 Preferred are regorafenib and the monohydrate of regorafenib, most preferred is regorafenib monohydrate as compounds of the present invention.

Due to the low solubility of regorafenib, in particular of regorafenib monohydrate in aqueous and oily vehicles standard solutions are not applicable. Also solutions containing tolerable amounts of emulsifiers, solubilising agents, complex forming excipients etc. are not available.

5 The topical ophthalmological pharmaceutical composition according to the invention comprises the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in a solid form, preferably in a crystalline form, more preferably in a microcrystalline form.

10 The minimum concentration of the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in the topical ophthalmological pharmaceutical composition is 0.1 %, preferably 0.2 % by weight of the total amount of the composition. The maximum concentration of the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in the topical ophthalmological pharmaceutical composition is 10 %, preferably 5 %, more preferably 3 % by weight of the total amount of the composition.

Preference is given to a concentration of the compound of the present invention in the pharmaceutical composition from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

15 Particular preference is given to a concentration of regorafenib in the pharmaceutical composition from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

Particular preference is given to a pharmaceutical composition resulting from addition of regorafenib monohydrate in amounts from 0.1 to 100 mg/ml, preferably from 1 to 50 mg/ml, more preferably from 2 to 40 mg/ml.

20 The topical ophthalmological pharmaceutical composition according to the invention includes but is not limited to eye drops, gels, ointments, dispersions or suspensions.

The compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate is used preferably in a micronized form.

25 Micronization can be achieved by standard milling methods, preferably by air jet milling, known to a skilled person. The micronized form can have a mean particle size of from 0.5 to 10 μm , preferably from 1 to 6 μm , more preferably from 2 to 3 μm . The indicated particle size is the mean of the particle size distribution measured by laser diffraction known to a skilled person (measuring device: HELOS, Sympatec).

30 One embodiment of the present invention is a topical ophthalmological pharmaceutical composition which is a suspension comprising the compound of the invention, preferably regorafenib, more preferably regorafenib monohydrate in a solid form, preferably in a crystalline form, more preferably in a microfine

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crystalline form suspended in an applicable pharmaceutically acceptable vehicle, and optionally further comprising one or more pharmaceutically acceptable excipients.

Suitable pharmaceutically acceptable vehicles according to the present invention include but are not limited to oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, hydrocarbon vehicles like liquid paraffin (Paraffinum liquidum, mineral oil), light liquid paraffin (low viscosity paraffin, Paraffinum perliquidum, light mineral oil), soft paraffin (vaseline), hard paraffin, vegetable fatty oils like castor oil, peanut oil or sesame oil, synthetic fatty oils like middle chain triglycerides (MCT, triglycerides with saturated fatty acids, preferably octanoic and decanoic acid), isopropyl myristate, caprylocaproyl macrogol-8 glyceride, caprylocaproyl polyoxyl-8 glycerides, wool alcohols like cetylstearylalcohols, wool fat, glycerol, propylene glycol, propylene glycol diesters of caprylic/capric acid, polyethyleneglycols (PEG), water like an aqueous isotonic sodium chloride solution or a mixture of thereof.

Preference is given non-aqueous and/or oily based pharmaceutically acceptable vehicles, preferably middle chain triglycerides (MCT, triglycerides with saturated fatty acids, preferably octanoic and decanoic acid, isopropyl myristate, caprylocaproyl macrogol-8 glyceride, caprylocaproyl polyoxyl-8 glycerides, oleoyl polyethyleneglycol glycerides, oleoyl macrogol-6 glycerides (Labrafil M 1944 CS), linoleoyl macrogol-6 glycerides (Labrafil M2125 CS = linoleoyl polyoxyl-6 glycerides), lauroyl macrogol-6 glycerides (Labrafil M 2130 CS = lauroyl polyoxyl-6 glycerides)), hydrocarbon vehicles, fatty oils like castor oil or a mixture of thereof, most preferably hydrocarbon vehicles like liquid paraffin or light liquid paraffin or a mixture thereof.

Very surprisingly the pharmaceutical composition according to the present invention comprising a lipophilic vehicle like liquid or light liquid paraffin provides by topical administration a sufficient amount of the active agent into the eye which is effective for treating ophthalmological disorders, although the solubility of regorafenib monohydrate in lipophilic vehicles is very low.

The pharmaceutically acceptable vehicle is the basis of the topical ophthalmological pharmaceutical composition according to the present invention and is present in the composition in a minimum concentration of 75%, preferably 80%, more preferably 85% and in a maximum concentration of 99.9%, preferably 99%, more preferably 98% by weight of the total amount of the composition.

The pharmaceutical composition according to the present invention may have different viscosities, so that in principle a range from low-viscosity system to pastes is conceivable. Preference is given to fluid systems which include low-viscosity and also higher-viscosity systems as long as they still flow under their own weight.

Suitable further pharmaceutically acceptable excipients used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to stabilizers, surfactants, polymer

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base carriers like gelling agents, organic co-solvents, pH active components, osmotic active components and preservatives.

Suitable stabilizers used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to colloidal silica, hydrophilic and hydrophobic silicas. Preference is given to hydrophobic silicas which are silicas which are not wetted by water; this means that they float on the water surface. Likewise suitable are hydrophobicized mixed oxides of silicon dioxide and aluminum oxide, but hydrophobic pure silicas are preferred. They are produced by mixing hydrophilic silica with silanes (halosilanes, alkoxysilanes, silazanes, siloxanes). This entails silanol groups being alkylated by alkyl groups preferably having up to 18 carbon atoms, particularly preferably having up to 8 carbon atoms, very particularly preferably having up to 4 carbon atoms, especially by methyl groups. Examples of silanes used in the production of hexamethyldisilazane or, preferably, dimethyldichlorosilane. The appropriate hydrophobic silicas may be derived from precipitated, colloidal, precompact or pyrogenic silicas, with preference for pyrogenic silicas. For example, reaction of a hydrophilic silica with dimethyldichlorosilane results in hydrophobic Aerosil having the proprietary name Aerosil® R 972; this has a degree of methylation of 66% - 75% (determined by titration of the remaining silanol groups).

The hydrophobic silica is employed in the formulations typically in a proportion of 0.1 - 10% by weight, preferably employed with 0.5 - 5% by weight of the total composition. Further suitable stabilizing and/or gelling agents used in the topical ophthalmic pharmaceutical composition according to the present invention include but are not limited to propylene glycol monopalmitostearate, glyceryl monostearate, glyceryl dibehenate, glyceryl distearate, hard fat, polyvinylpyrrolidone, polyethylene, glycerol, polyoxyethylene stearates, sorbitan fatty acid esters, cholesterol, macrogol-20-glycerolmonostearate, poloxamer 124, isopropyl myristate, isopropyl palmitate, colloidal silica, hydrophobic colloidal silica, magnesium stearate, zinc stearate, aluminium stearate, lanolin alcohols, organoclays, petrolatum, polyoxyl 6 stearate.

Suitable surfactants used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to lipids such as phospholipids, phosphatidylcholines, lecithin, cardiolipins, fatty acids, phosphatidylethanolamines, phosphatides, tyloxapol, polyethylenglycols and derivatives like PEG 400, PEG 1500, PEG 2000, poloxamer 407, poloxamer 188, polysorbate 80, polysorbate 20, sorbitan laurate, sorbitan stearate, sorbitan palmitate or a mixture thereof, preferably polysorbate 80.

Suitable polymer base carriers like gelling agents used in the topical ophthalmological pharmaceutical composition according to the present invention include but are not limited to cellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethyl cellulose (CMC), methylcellulose (MC), hydroxyethylcellulose (HEC), amylase and derivatives, amylopectins and

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derivatives, dextran and derivatives, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and acrylic polymers such as derivatives of polyacrylic or polymethacrylic acid like HEMA, carbopol or a mixture thereof.

Suitable organic co-solvents used in the pharmaceutical composition according to the invention include
5 but are not limited to ethylene glycol, propylene glycol, N-methyl pyrrolidone, 2-pyrrolidone, 3-pyrrolidinol, 1,4-butanediol, dimethylglycol monomethylether, diethyleneglycol monomethylether, solketal, glycerol, polyethylene glycol, polypropylene glycol.

Suitable pH active components such as buffering agents or pH-adjusting agents used in the pharmaceutical composition according to the invention include but are not limited to disodium phosphate, monosodium
10 phosphate, boric acid, sodium borate, sodium citrate, hydrochloric acid, sodium hydroxide.

The pH active components are chosen based on the target pH for the composition which generally ranges from pH 4 - 9.

Suitable osmotic active components used in the pharmaceutical composition according to the invention include but are not limited to sodium chloride, mannitol, glycerol.

15 Preservatives used in the pharmaceutical composition according to the invention include but are not limited to benzalkonium chloride, alkyl dimethylbenzylammonium chloride, cetrimide, cetylpyridinium chloride, benzododecinium bromide, benzethonium chloride, thiomersal, chlorobutanol, benzyl alcohol, phenoxethanol, phenylethyl alcohol, sorbic acid, methyl and propyl parabens, chlorhexidine digluconate, EDTA or mixtures thereof.

20 Gelling agents, pH active agents and osmotic active agents are preferably used in the case of an aqueous pharmaceutically acceptable vehicle.

The amount of the suitable further pharmaceutically acceptable excipient in the suspension according to the present invention can be from 0.1 to 15 %, preferably from 0.5 to 10 %, more preferably from 1 to 5 % by the total weight of the suspension.

25 Preferably the amount of hydroxypropylmethylcellulose in the suspension according to the present invention can be from 0.05 to 15 %, preferably from 0.1 to 10 %, more preferably from 1 to 5 % by the total weight of the suspension.

30 Preferably the amount of polysorbate 80 in the suspension according to the present invention can be from 0.05 to 10 %, preferably from 0.1 to 7 %, more preferably from 0.5 to 4 % by the total weight of the suspension.

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Preference is given to a topical ophthalmological pharmaceutical composition comprising crystalline regorafenib monohydrate, more preferably microcrystalline regorafenib monohydrate in a concentration of 0.1 to 10 %, more preferably 0.2 to 5 % weight of the total amount of the composition suspended in a pharmaceutically acceptable vehicle selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof.

Preference is also given to a topical ophthalmological pharmaceutical composition comprising crystalline regorafenib monohydrate, more preferably microfine crystalline regorafenib monohydrate in a concentration of 0.1 to 10 %, more preferably 0.2 to 5 % weight of the total amount of the composition suspended in oleoyl polyethyleneglycol glyceride as pharmaceutically acceptable vehicle.

The total amount of the active agent to be administered via the topical route into the eye using the pharmaceutical composition of the present invention will generally range from about 0.01 to 50 mg, preferably 0.02 to 10 mg, more preferably 0.05 to 5 mg per administration and per eye. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of ophthalmological disorders, by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art. The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

The pharmaceutical composition according to the invention is administered one or more, preferably up to 5, more preferably up to 3 times per day.

The typical method of administration of the pharmaceutical composition according to the invention is the topical delivery into the eye.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on individual response to the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by preferably topical administration into the eye to a patient in need thereof, and will have advantageous properties in terms

of drug release, bioavailability, and/or compliance in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

The pharmaceutical composition according to the invention is chemically stable for more than 18 months, preferably more than 24 months. Chemically stable according the present invention means that the active agent does not degrade significantly ($< 0.6\%$) during storage.

In other words the topical ophthalmological pharmaceutical composition according to the invention contains 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide in an amount of equal or less than 0.05% , that means from 0.0001% to a maximum of 0.05% , preferably in an amount of equal or less than 0.025% , that means from 0.0001% to a maximum of 0.025% , most preferably in an amount of equal or less than 0.01% , that means from 0.0001% to a maximum of 0.01% by weight based on the amount of the compound of the formula (I).

Process for manufacturing

Various methods can be used to prepare the ophthalmological pharmaceutical composition according to the invention. First the pharmaceutically acceptable vehicle is prepared by optionally mixing the applicable vehicle or mixture of vehicles with the pharmaceutically acceptable excipients. Thereafter the active agent is dispersed or suspended into said mixture. The process may also include sterilization e.g. by sterile precipitation, gamma irradiation, sterile filtration, heat sterilization, aseptic filling, or a combination of such optional steps.

The present invention also relates to a process for the manufacturing of a topical ophthalmological pharmaceutical composition according to the invention, wherein the compound of the present invention is suspended in an applicable pharmaceutically acceptable vehicle optionally in the presence of further one or more pharmaceutically acceptable excipients and the suspension is homogenized.

Preference is given to a process for the manufacturing of a topical ophthalmological pharmaceutical composition according to the invention, wherein

- a) the applicable pharmaceutically acceptable vehicle or a mixture of applicable pharmaceutically acceptable vehicles is prepared by mixing the vehicles optionally in the presence of a further one or more pharmaceutically acceptable excipients,
- b) the compound of the present invention, preferably regorafenib, more preferably regorafenib monohydrate, is suspended into said applicable pharmaceutically acceptable vehicle for example at room temperature, optionally in the presence of a further one or more pharmaceutically acceptable excipients,

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- c) the suspension is homogenized by stirring, shaking or vortexing, preferably stirring, at room temperature,
- d) the suspension is subdivided into single units and filled into applicable vials, container, tube, flask, dropper and/or syringe.

5 Optionally in step a) the further one or more pharmaceutically acceptable excipients are added to the applicable pharmaceutically acceptable vehicle at elevated temperatures for example of 40 to 70°C.

Method of treating ophthalmological disorders

The present invention also relates to a use of the pharmaceutical composition according to the invention to treat or prevent ophthalmological disorders.

- 10 Examples of ophthalmological disorders according to the invention include but are not limited to age-related macular degeneration (AMD), choroidal neovascularization (CNV), retinal detachment, diabetic retinopathy, atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), diabetic macular edema, retinal vein occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, angiogenesis in the front of the
- 15 eye like corneal angiogenesis following e.g. keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.

Examples of age-related macular degeneration (AMD) include but are not limited to dry or nonexudative AMD, or wet or exudative or neovascular AMD.

- 20 Preference is given to age-related macular degeneration (AMD) like dry AMD, wet AMD or choroidal neovascularization (CNV).

The pharmaceutical composition according to the invention can be administered as the sole pharmaceutical composition or in combination with one or more other pharmaceutical compositions or active agents where the combination causes no unacceptable adverse effects.

- 25 "Combination" means for the purposes of the invention not only a dosage form which contains all the active agents (so-called fixed combinations), and combination packs containing the active agents separate from one another, but also active agents which are administered simultaneously or sequentially, as long as they are employed for the prophylaxis or treatment of the same disease.

- Since the combination according to the invention is well tolerated and is potentially effective even in low
- 30 dosages, a wide range of formulation variants is possible. Thus, one possibility is to formulate the individual active ingredients of the combination according to the invention separately. In this case, it is

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not absolutely necessary for the individual active ingredients to be taken at the same time; on the contrary, sequential intake may be advantageous to achieve optimal effects. It is appropriate with such separate administration to combine the formulations of the individual active ingredients simultaneously together in a suitable primary packaging. The active ingredients are present in the primary packaging in each case in separate containers which may be, for example, tubes, bottles or blister packs. Such separate packaging of the components in the joint primary packaging is also referred to as a kit.

In one embodiment, the pharmaceutical compositions of the present invention can be combined with other ophthalmological agents. Examples of such agents include but are not limited to carotenoids like lycopene, lutein, zeaxanthin, phytoene, phytofluene, carnosic acid and derivatives thereof like carnosol, 6,7-dehydrocarnosic acid, 7-ketocarnosic acid, a zinc source like zinc oxide or a zinc salt like its chloride, acetate, gluconate, carbonate, sulphate, borate, nitrate or silicate salt, copper oxide, vitamin A, vitamin C, vitamin E and/or β -carotene.

In another embodiment, the pharmaceutical compositions of the present invention can be combined with other signal transduction inhibitors targeting receptor kinases of the domain families of e.g. VEGFR, PDGFR, FGFR and their respective ligands or other pathway inhibitors like VEGF-Trap (aflibercept), pegaptanib, ranibizumab, pazopanib, bevasiranib, KH-902, mecamlamine, PF-04523655, E-10030, ACU-4429, volociximab, sirolimus, fenretinide, disulfiram, sonepcizumab and/or tandospirone. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as STI-571 / Gleevec (Zvelebil, Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 2000, 2(1), 74-82), PTK-787 (Wood et al., Cancer Res. 2000, 60(8), 2178-2189), SU-11248 (Demetri et al., Proceedings of the American Society for Clinical Oncology 2004, 23, abstract 3001), ZD-6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, March 24-28, 2001, abstract 3152), AG-13736 (Herbst et al., Clin. Cancer Res. 2003, 9, 16 (suppl 1), abstract C253), KRN-951 (Taguchi et al., 95th AACR Meeting, Orlando, FL, 2004, abstract 2575), CP-547,632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673,451 (Roberts et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 2130), MLN-518 (Shen et al., Blood 2003, 102, 11, abstract 476), and AZD-2171 (Hennequin et al., Proceedings of the American Association of Cancer Research 2004, 45, abstract 4539), PKC412, nepafenac.

Preference is given to a combination with bevacizumab, aflibercept, pegaptanib, ranibizumab, pazopanib and/or bevasiranib.

Generally, the use of the other ophthalmological agents in combination with the pharmaceutical compositions of the present invention will serve to:

(1) yield better efficacy as compared to administration of either agent alone,

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- (2) provide for the administration of lesser amounts of the administered agents,
- (3) provide for treating a broader spectrum of mammals, especially humans,
- (4) provide for a higher response rate among treated patients,
- (5) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other agent combinations produce antagonistic effects. It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

10 All publications, applications and patents cited above and below are incorporated herein by reference.

The weight data are, unless stated otherwise, percentages by weight and parts are parts by weight.

Examples:

HPLC Methods:

Two separate HPLC methods were developed for the determination of regorafenib content, unidentified degradation products and unidentified secondary components, as well as for the determination of the specific degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA), respectively, within pharmaceutical formulations.

1) HPLC method for the determination of regorafenib content, unidentified secondary components, and unidentified degradation products: Samples were prepared by dilution of drawn formulation aliquots with water/acetonitrile (25/75) to a final regorafenib concentration of 100µg/ml. 10µl of each sample were injected into an Agilent 1100 HPLC system (Agilent, Waldbronn, Germany), and samples were run on a heated (40°C) Symmetry C18 column (150 x 4,6mm - 3,5µm particle size, Waters, Eschborn, Germany) applying a flow rate of 1ml/min. The mobile phase consisted of a mixture of potassium phosphate buffer pH 2.4 (A) and acetonitrile/ethanol (6/4) (B). The following gradient was applied: minute 0: A, 60% / B, 40%; minute 12: A, 20% / B, 80%; minute 16: A, 20% / B, 80%; minute 16.5: A, 60% / B, 40%; minute 20: A, 60% / B, 40%. Regorafenib, unidentified secondary components, and unidentified degradation products were quantified using a DAD detector at a wavelength of 265 nm. Regorafenib content (column 3 in tables below) within formulations was quantified by using an external 2-point calibration straight line. Unidentified secondary components and unidentified degradation products (columns 5-7 in tables below) are described as % of summarized sample-related peak areas. Precision of the system was

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determined with each sample set run, by six times injection of a 100% regorafenib standard (e.g. 100µg/ml), coefficient of variation of peak areas resulting from these six injections was always below 2%. Relative Y-axis intercept of a 2-point (e.g. 50µg/ml, 100µg/ml) calibration straight line was always below 3% (referring to 100% Regorafenib standard). The regorafenib peak appears at 11.5 minutes.

- 5 2) HPLC method for the determination of the specific degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA). Samples were prepared by dilution of drawn formulation aliquots with acetone to a final regorafenib concentration of 3000µg/ml. 15µl of each sample were injected into an Agilent 1100 HPLC system (Agilent, Waldbronn, Germany), and samples kept at 10° in the autosampler were run on a Symmetry C18 column (150 x 4,6mm - 3,5µm particle size, 10 Waters, Eschborn, Germany) held at 20°C with a flow rate of 1ml/min. The mobile phase consisted of a mixture of potassium phosphate buffer pH 2.4 (A) and acetonitrile/ethanol (6/4) (B). The following gradient was applied: minute 0: A, 62% / B, 38%; minute 5: A, 44% / B, 56%; minute 5.01: A, 15% / B, 85%; minute 9: A, 15% / B, 85%; minute 9.01: A, 62% / B, 38%; minute 12: A, 62% / B, 38%. 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (column 4 in tables below) was 15 quantified using a DAD detector at a wavelength of 232 nm, referring to an external 3-point (e.g. 0.04µg/ml, 0.1µg/ml, 1µg/ml) calibration straight line. The 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide peak appears at 3.9 minutes. Limit of detection (LOD) and limit of quantification (LOQ) of 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide were determined for two different matrices (water and paraffin), and were: LOD: 4ppm (water), 13ppm 20 (paraffin); LOQ: 13ppm (water) and 43ppm (paraffin).

Example 1: Ophthalmological suspension comprising regorafenib monohydrate in oleoyl polyethyleneglycol glyceride (20 mg/ml)

- 200 mg of micronized regorafenib monohydrate was suspended in oleoyl polyethyleneglycol glyceride 25 (10 ml). The suspension was homogenized by stirring at room temperature for 15 minutes.

- Stability of regorafenib in oleoyl polyethyleneglycol glyceride was tested at a concentration of 3 mg/ml over 4 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 95.0-101% of theoretical concentration, largest unidentified degradation product ranged from 0.3 to 0.7%. 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA) content was 30 below < 13 ppm (< LOD determined for paraffin based formulation, Table 2). For analytical details see HPLC Method section above.

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Table 2. Content and stability of regorafenib within oleoyl polyethyleneglycol glyceride based formulation:

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (ppm referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		95.0	< 13	0.04	0.04	0.7
1 day	25°C / 60% r.h.	101	< 13	0.04	0.04	0.6
4 weeks	25°C / 60%r.h.	99.0	< 13	0.04	0.04	0.3
4 weeks	40°C / 75%r.h.	98.7	< 13	0.04	0.04	0.3

Example 2: Ophthalmological suspension comprising regorafenib monohydrate in liquid paraffin (20 mg/ml)

5 400 mg of micronized regorafenib monohydrate was suspended in 20 ml of light liquid paraffin. The suspension was homogenized by stirring at room temperature for 15 minutes.

Stability of the suspension was tested at a concentration of 20mg/ml over 13 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 74.8-99.6% of theoretical concentration. The observed fluctuation is most likely due to inhomogeneity of the sample after manual shaking of the suspension. No unidentified degradation product was observed in chromatograms. AFP-PMA content was below < 43 ppm (< LOQ determined for paraffin based formulation, Table 3). For analytical details see Analytics section above.

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Table 3. Content and stability of regorafenib within paraffin based formulation.

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (ppm referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		99.6	< 43	0.04	0.04	-
4 weeks	25°C/60 %r.h.	85.4	< 43	0.04	0.04	-
4 weeks	40°C/75 %r.h.	74.8	< 43	0.04	0.04	-
13 weeks	25°C/60 %r.h.	96.9	< 43	0.04	0.04	-
13 weeks	40°C/75 %r.h.	94.6	< 43	0.04	0.04	-

Example 3: Ophthalmological suspension comprising regorafenib monohydrate and 0.5% hydrophobic colloidal silica in liquid paraffin (20 mg/ml)

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- 0.25 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (50 ml) by stirring at room temperature to prepare the suspending vehicle (0.5% (w/v) hydrophobic colloidal silica in light liquid paraffin). 200 mg of regorafenib monohydrate was added to an aliquot of the suspending vehicle (10 ml) and the suspension was homogenized for 45 min. using a vibration mill at a frequency of 9.1 s⁻¹.
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- Afterwards, the suspension was filled into glass vials (approximately 6 ml per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps.

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Stability of the suspension was tested over 4 weeks at 4°C, room temperature (approx. 25°C) and 40°C/ 75% relative humidity (see Table 4).

Table 4. Content and stability of Regorafenib within Example 3 formulation

Storage condition	Content Regorafenib (g/l)	Content Regorafenib (% of theoretical)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
4°C	21.07	105.4	0.05	<0.005	0.05
RT	24.13	120.7	0.05	<0.005	0.05
40°C/ 75 % r.h.	19.41	97.1	<0.05	<0.005	<0.05

Example 4: Ophthalmological suspension comprising regorafenib monohydrate and 2% hydrophobic colloidal silica in liquid paraffin (20 mg/ml)

1 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (50 mL) by stirring at room temperature to prepare the suspending vehicle (2% (w/v) hydrophobic colloidal silica in light liquid paraffin). 200 mg of regorafenib monohydrate was added to an aliquot of the suspending vehicle (10 mL) and the suspension was homogenized for 45 min. using a vibration mill at a frequency of 9.1 s⁻¹.

Afterwards, the suspension was filled into glass vials (approximately 6 mL per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps.

Stability of the suspension was tested over 4 weeks at 4°C, room temperature (approx. 25°C) and 40°C/ 75% relative humidity (see Table 5).

Table 5. Content and stability of Regorafenib within Example 4 formulation

Storage condition	Content Regorafenib (g/l)	Content Regorafenib (% of theoretical)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
4°C	20.01	100.1	<0.05	<0.005	<0.05
RT	21.84	109.2	0.05	<0.005	0.05
40°C/ 75 % r.h.	22.67	113.4	0.05	<0.005	0.05

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Example 5: Ophthalmological suspension comprising regorafenib monohydrate and 5% hydrophobic colloidal silica in liquid paraffin (20 mg/ml)

2.5 g of hydrophobic colloidal silica (Aerosil® R972) was dispersed in light liquid paraffin (50 mL) by stirring at room temperature to prepare the suspending vehicle (5% (w/v) hydrophobic colloidal silica in light liquid paraffin). 200 mg of regorafenib monohydrate was added to an aliquot of the suspending vehicle (10 mL) and the suspension was homogenized for 45 min. using a vibration mill at a frequency of 9.1 s⁻¹.

Afterwards, the suspension was filled into glass vials (approximately 6 mL per vial) and the vials were closed with rubber stoppers and sealed with aluminium crimp caps.

Stability of the suspension was tested over 4 weeks at 4°C, room temperature (approx. 25°C) and 40°C/ 75% relative humidity (see Table 6).

Table 6. Content and stability of Regorafenib within Example 5 formulation

Storage condition	Content Regorafenib (g/l)	Content Regorafenib (% of theoretical)	Degradation product/ max. single (%)	AFP-PMA content (%)	Degradation products/ sum (%)
4°C	19.14	95.7	<0.05	<0.005	<0.05
RT	18.55	92.8	<0.05	<0.005	<0.05
40°C/ 75 % r.h.	18.76	93.8	<0.05	<0.005	<0.05

Example 6: Ophthalmological suspension comprising regorafenib monohydrate in water based vehicle (20 mg/ml)

1.7 g of hydroxypropymethylcellulose 15 cp (HPMC) was dispersed in isotonic sodium chloride solution (48 g, 0.9% NaCl in water) at 70°C. The mixture was cooled down to room temperature while stirring. At room temperature evaporated water, and subsequently polysorbate 80 (0.5 g) was added and dissolved under moderate stirring. 518 mg of regorafenib monohydrate was added to an aliquot of the prepared vehicle (24.5g) and the suspension was homogenized by gently stirring at room temperature for 15 minutes.

Stability of the suspension was tested at a concentration of 10 mg/ml over 13 weeks at 25°C, 60% relative humidity (r.h.) and 40°C, 75% r.h.. Regorafenib content ranged between 103-112% of theoretical concentration. The observed fluctuation is most likely due to inhomogeneity of the sample after manual shaking of the suspension. Largest unidentified degradation product was < 0.1% of summarized sample related peak areas. Amount of AFP-PMA was determined only after 9 weeks storage.

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Table 7. Content and Stability of Regorafenib within water based formulation.

1	2	3	4	5	6	7
Storage time	Storage condition	regorafenib content (% of theoretical), via external calibration	AFP-PMA content (ppm referring to Regorafenib), via external calibration	Largest unidentified secondary component in standard (% of summarized peak areas)	Largest unidentified secondary component in sample (% of summarized peak areas)	Largest unidentified degradation product in sample (% of summarized peak areas)
0		103	n.d.	0.04	0.04	-
4 weeks	25°C/60 %r.h.	104	n.d.	0.1	0.04	-
4 weeks	40°C/75 %r.h.	112	n.d.	0.1	0.04	-
9 weeks	25°C/60 %r.h.		56			
9 weeks	40°C/75 %r.h.		86			
13 weeks	25°C/60 %r.h.	104	n.d.	0.06	0.04	-
13 weeks	40°C/75 %r.h.	104	n.d.	0.06	0.04	-

In tables 2, 3 and 7 above column 5 describes the percental amount of the largest unidentified secondary component in the standard used in the HPLC method to be compared with the value of column 6 which describes the percental amount of the same unidentified secondary component in the formulation. Column 7 describes the percental amount of the largest unidentified degradation product in the formulation which

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is not AFP-PMA. Said degradation product is not detectable in the standard but is formed in the formulation.

Example 7: Topical efficacy of different formulations containing regorafenib in the laser-induced choroidal neovascularization (CNV) model

- 5 The aim of this study was to determine whether twice daily topical administration (eye drops) of the topical ophthalmological pharmaceutical compositions according to the invention results in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation (Dobi et al, Arch. Ophthalmol. 1989, 107(2), 264-269 or Frank et al, Curr. Eye Res. 1989 Mar, 8(3), 239-247)
- 10 For this purpose, a total of 44 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly assigned to eight groups of six to eight animals each. On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg / kg xylazine and 80 mg / kg ketamine (dissolved in water containing 5 mg/ml chlorobutanol hemihydrate and propylenglycol) After instillation of one drop of 0.5 % atropin (dissolved in 0.9 % saline containing Benzalkoniumchloride) to dilate the pupils,
- 15 choroidal neovascularisation was induced by burning six holes in the retina (disruption of Bruch's membrane) of one eye per animal (lesion size: 50 µm, laser intensity: 150 mW; stimulus duration: 100 ms) using a 532 nm argon laser.

The following formulations were included:

- a) 100 % oleoyl polyethyleneglycol glycerides as used in example 1 (vehicle control), n=8
- 20 b) Example 1 (20 mg/ml, suspension), n=8
- c) 100 % light liquid paraffin as used in example 2 (vehicle control), n=8
- d) Example 2 (20 mg/ml, suspension), n=8
- e) Water-based vehicle (Hydroxypropymethylcellulose 15 cp 3.5%, polysorbate 80 0.5%, isotonic NaCl solution 96% (vehicle control), n=6
- 25 f) Example 3 (20 mg/ml, suspension), n=6

Of each formulation, 10 µl were applied to the affected eye twice daily at an 10:14 hour interval during the complete observation period of 23 days. The body weight of all animals was recorded before the start and once daily during the study. An angiography was performed on day 21 using a fluorescence fundus camera (Kowe Genesis Df, Japan). Here, after anesthesia and pupillary dilation, 10 % sodium fluorescein

30 (dye, dissolved in water) was subcutaneously injected and pictures were recorded 2 and 10 min after dye

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injection. The vascular leakage of the fluorescein on the angiograms was evaluated by three different examiners who were blinded for group allocation (examples 1 to 3 versus respective vehicle). Each lesion was scored with 0 (no leakage) to 3 (strongly stained), and a mean from all 6 lesions was used as the value for the respective animal. On day 23, animals were sacrificed and eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, and the sclera-choroid complex was washed, blocked and stained with a FITC-isolectine B4 antibody in order to visualize the vasculature. Then, the sclera-choroids were flat-mounted and examined under a fluorescence microscope (Keyence Biozero) at 488 nm excitation wavelength. The area (in μm^2) of choroidal neovascularization was measured using ImageTool software.

Results:

A) Efficacy regarding vascular leakage (angiography scores day 21):

Fig. 1: Angiography scores of vehicle (oleoyl polyethyleneglycol glycerides (Labrafil), formulation a) and regorafenib (example 1, formulation b) treated animals at day 21. Data are presented as mean $\pm$ SD, p-value according to t-test. N=8 per group.

Table 8: Raw data of the histogram depicted in Fig. 1. Single values represent the means from three different observers blinded with respect to treatment.

Animal	100% oleoyl polyethyleneglycol glycerides (formulation a)	Example 1 (formulation b)
1	1,80	1,14
2	1,72	0,67
3	1,63	1,44
4	1,72	0,90
5	1,67	1,00
6	2,00	1,22
7	1,56	1,33
8	2,33	1,33

Fig. 2: Angiography scores of vehicle (paraffin, formulation c) and regorafenib (example 2, formulation d) treated animals at day 21. Data are presented as mean $\pm$ SD, p-value according to t-test. N=8 per group.

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Table 9: Raw data of the histogram depicted in Fig. 2. Single values represent the means from three different observers blinded with respect to treatment.

Animal	100% paraffin (formulation c)	Example 2 (formulation d)
1	2,33	1,29
2	1,77	1,78
3	1,50	0,69
4	1,91	1,34
5	2,21	0,67
6	2,06	1,00
7	2,10	0,96
8	2,54	1,51

Fig. 3: Angiography scores of vehicle (water based, formulation e) and regorafenib (example 3, formulation f) treated animals at day 21. Data are presented as mean ± SD, p-value according to t-test. N=6 per group.

Table 10: Raw data of the histogram depicted in Fig. 3. Single values represent the means from three different observers blinded with respect to treatment.

Animal	formulation e	Example 3 (formulation f)
1	1,61	1,78
2	1,78	1,60
3	1,93	1,34
4	2,27	2,00
5	1,49	0,80
6	2,10	2,20

B) Efficacy regarding neovascularization (neovascular area day 23):

Fig. 4: Neovascular area of vehicle (oleoyl polyethyleneglycol glycerides (Labrafil), formulation a) and regorafenib (example 1, formulation b) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

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Table 11: Raw data of the histogram depicted in Fig. 4. Single values represent the means from all six lesions.

Animal	100 % oleoyl polyethyleneglycol glycerides (formulation a)	Example 1 (formulation b)
1	134507	90562
2	70878	59819
3	84254	67222
4	86071	72584
5	93586	30455
6	69696	47866
7	103307	23991
8	98472	63033

Fig. 5: Neovascular area of vehicle (paraffin, formulation c) and regorafenib (example 2, formulation d) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=8 per group.

Table 12: Raw data of the histogram depicted in Fig. 5. Single values represent the means from all six lesions.

Animal	100 % paraffin (formulation c)	Example 2 (formulation d)
1	105910	62047
2	81060	70927
3	98735	84481
4	85019	80151
5	98071	70568
6	101668	59804
7	99413	63145
8	113797	91466

Fig. 6: Neovascular area of vehicle (water based, formulation e)) and regorafenib (example 3, formulation f) treated animals at day 23. Data are presented as mean ± SD, p-value according to t-test. N=5 per group.

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Table 13: Raw data of the histogram depicted in Fig. 6. Single values represent the means from all six lesions.

Animal	formulation e	Example 3 (formulation f)
1	78759	107547
2	83420	117379
3	96239	72404
4	107654	99371
5	87960	91977

In both groups, one flatmount preparation each could not be scored due to poor tissue quality.

5 Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

What is claimed is:

1. A topical ophthalmological pharmaceutical composition comprising regorafenib, a hydrate, solvate or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof as active agent and at least one pharmaceutically acceptable vehicle.
- 5 2. The pharmaceutical composition of claim 1 containing regorafenib monohydrate as active agent.
3. The pharmaceutical composition of any of claims 1 to 2 wherein the active agent is in a solid form.
4. The pharmaceutical composition of any of claims 1 to 3 wherein the active agent is in a crystalline form.
- 10 5. The pharmaceutical composition of any of claims 1 to 4 wherein the active agent is in a microcrystalline form.
6. The pharmaceutical composition of any of claims 1 to 5 wherein the concentration of the active agent in the pharmaceutical composition is from 0.1 to 10% by weight of the total amount of the composition.
- 15 7. The pharmaceutical composition of any of claims 1 to 5 wherein the concentration of the active agent in the pharmaceutical composition is from 0.1 to 100 mg/ml.
8. The pharmaceutical composition of any of claims 1 to 5 in form of eye drops, gels, ointments, dispersions or suspensions.
9. The pharmaceutical composition of any of claims 1 to 5 which is a suspension comprising the active agent suspended in an applicable pharmaceutically acceptable vehicle.
- 20 10. The pharmaceutical composition of claim 9 wherein the pharmaceutically acceptable vehicle is selected from the group comprising oleoyl polyethyleneglycol glycerides, linoleoyl polyethyleneglycol glycerides, lauroyl polyethyleneglycol glycerides, liquid paraffin, light liquid paraffin, soft paraffin (vaseline), hard paraffin, castor oil, peanut oil, sesame oil, middle chain triglycerides, cetylstearylalcohols, wool fat, glycerol, propylene glycol, polyethyleneglycols (PEG) or
25 a mixture of those, water or a mixture thereof.

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11. The pharmaceutical composition of claim 10 wherein the pharmaceutically acceptable vehicle is selected from the group comprising liquid paraffin, light liquid paraffin or a mixture thereof.
12. The pharmaceutical composition of any of claims 1 to 11 comprising further pharmaceutically acceptable excipients like stabilizers, surfactants, polymer base carriers like gelling agents, organic
5 co-solvents, pH active components, osmotic active components and preservatives.
13. The pharmaceutical composition of claim 12 wherein the stabilizer is a hydrophobic silica.
14. The pharmaceutical composition of claim 13 comprising hydrophobic silica in an amount of 0.1 % to 10 % by weight of the total composition.
15. A combination comprising the pharmaceutical composition according to any of claims 1 to 14
10 combined with one or more further active agents.
16. A process for manufacturing a pharmaceutical composition according to any of claims 1 to 14 wherein the active agent is suspended in an applicable pharmaceutically acceptable vehicle optionally in the presence of further one or more pharmaceutically acceptable excipients and the suspension is homogenized.
- 15 17. The pharmaceutical composition of any of claims 1 to 14 for the use of treating or preventing an ophthalmological disorder selected from the group comprising age-related macular degeneration (AMD), choroidal neovascularization (CNV), retinal detachment, diabetic retinopathy, atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), diabetic macular edema, retinal vein occlusion, choroidal retinal vein
20 occlusion, macular edema, macular edema due to retinal vein occlusion, angiogenesis in the front of the eye, corneal angiogenesis following keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.
18. The pharmaceutical composition of claim 17 for the use of treating or preventing an
25 ophthalmological disorder selected from the group comprising dry AMD, wet AMD or choroidal neovascularization (CNV).
19. Method for using the pharmaceutical composition according to any of claims 1 to 14 to treat or prevent an ophthalmological disorder selected from the group comprising age-related macular degeneration (AMD), choroidal neovascularization (CNV), retinal detachment, diabetic
30 retinopathy, atrophic changes of the retinal pigment epithelium (RPE), hypertrophic changes of the retinal pigment epithelium (RPE), diabetic macular edema, retinal vein occlusion, choroidal retinal vein occlusion, macular edema, macular edema due to retinal vein occlusion, angiogenesis

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- 27 -

in the front of the eye, corneal angiogenesis following keratitis, corneal transplantation or keratoplasty, corneal angiogenesis due to hypoxia (extensive contact lens wearing), pterygium conjunctivae, subretinal edema and intraretinal edema.

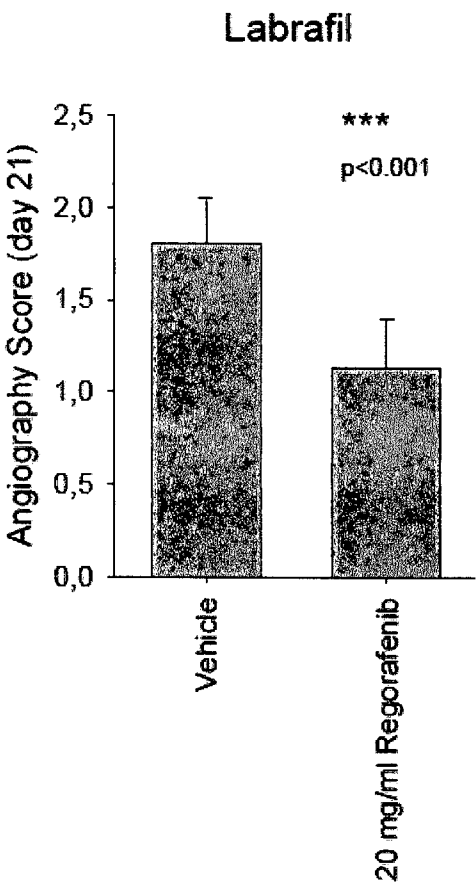
Topical Ophthalmological Composition containing Regorafenib

Abstract

The present invention relates to topical ophthalmological pharmaceutical compositions containing regorafenib, a hydrate, solvate or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating ophthalmological disorders.

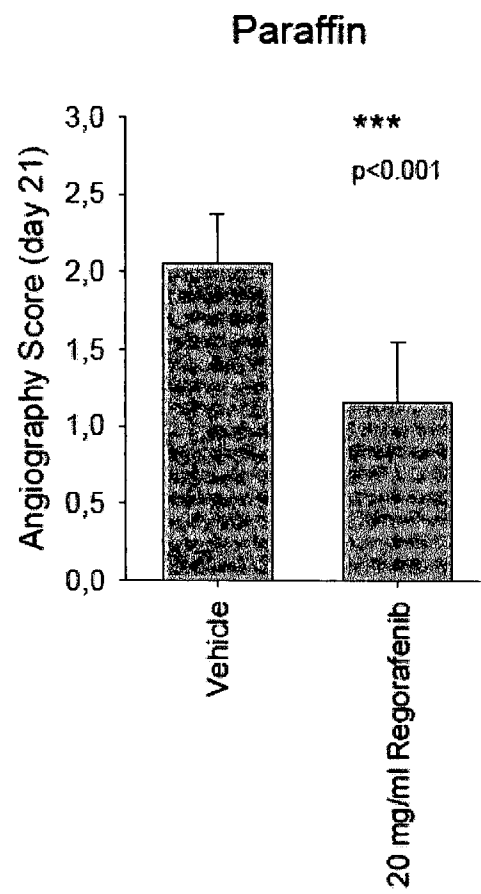
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Figure 1



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Figure 2



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Figure 3

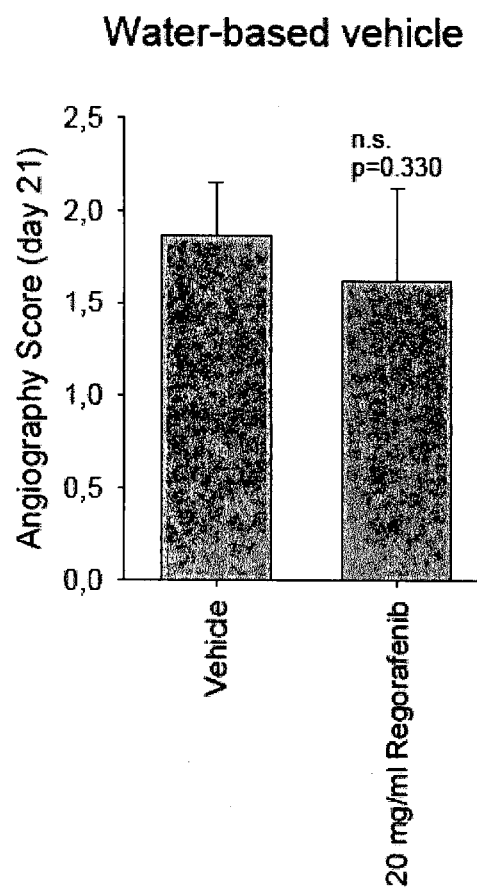
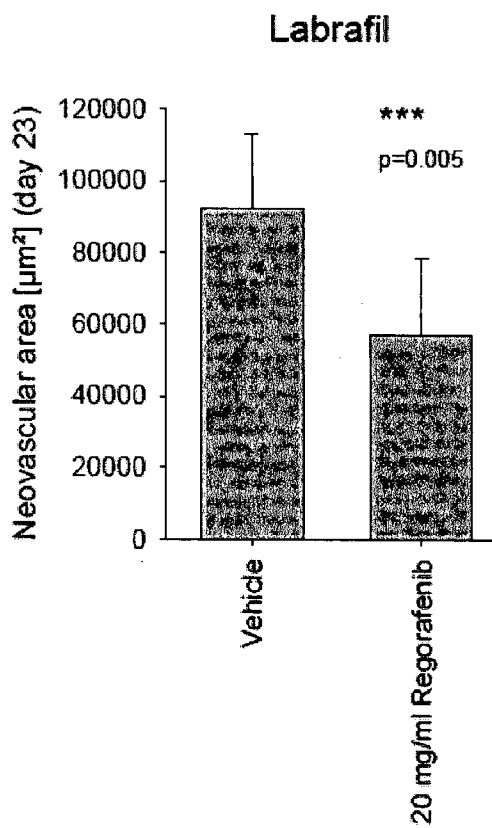
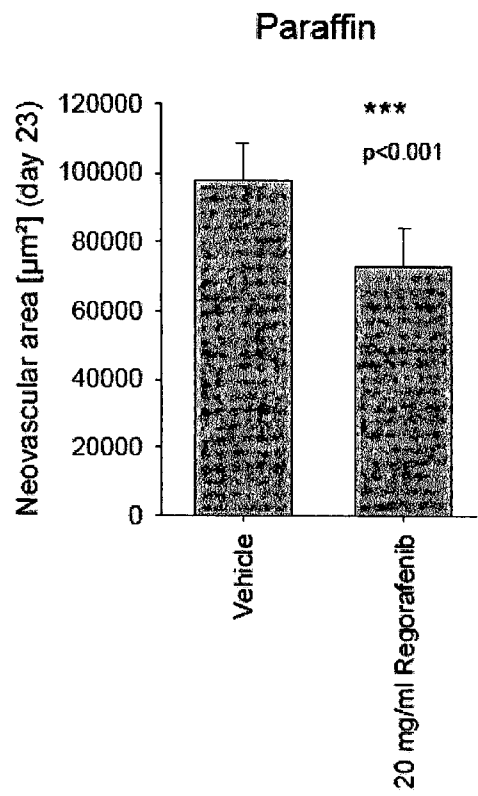


Figure 4



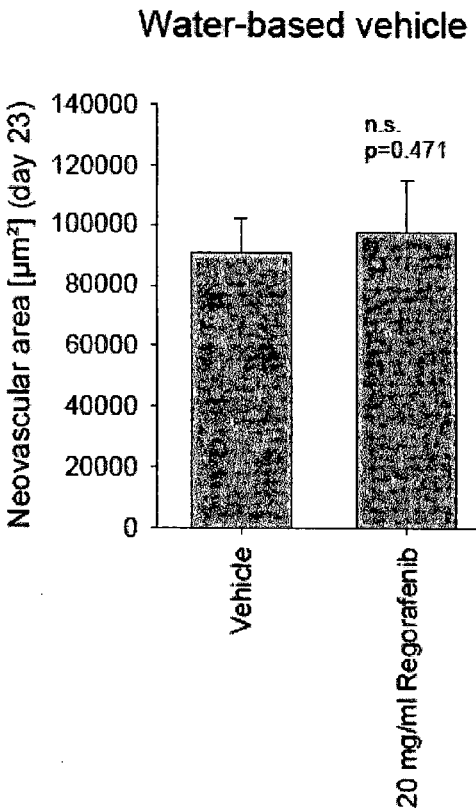
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Figure 5



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Figure 6



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CONSIGNACION	BANCO DE BOGOTA	062754387	651475230	23/12/2013	9.585.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	500.000.00	500.000.00
				\$500.000.00

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No. 13-300167- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 188 189

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CONSIGNACION	BANCO DE BOGOTA	062754387	651475230	23/12/2013	9.585.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
11 50005-01-01	SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	330.000.00
				\$330.000.00

SON: **TRESCIENTOS TREINTA MIL PESOS MONEDA CORRIENTE***

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PATENTE DE INVENCION ☐

MODELO DE U

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

☐	Indicación que se solicita una PCT
☐	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☐	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐